US 20190048072A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2019/0048072 A1**

Ligueros-Saylan et al. (43) **Pub. Date: Feb. 14, 2019**

(54) **USE OF IL-1BETA BINDING ANTIBODIES**

(71) Applicant: **Novartis AG**, Basel (CH)

(72) Inventors: **Monica Ligueros-Saylan**, East Hanover, NJ (US); **Patrice Matchaba**, East Hanover, NJ (US); **Tom Thuren**, East Hanover, NJ (US); **Paul Ridker**, Boston, MA (US); **Peter Libby**, Boston, MA (US); **Penelope OTTEWELL**, Sheffield (GB); **Yi Yang LAU**, East Hanover, NJ (US); **Margaret DUGAN**, East Hanover, NJ (US)

(21) Appl. No.: **15/970,542**

(22) Filed: **May 3, 2018**

Related U.S. Application Data

(60) Provisional application No. 62/649,631, filed on Mar. 29, 2018, provisional application No. 62/596,054, filed on Dec. 7, 2017, provisional application No. 62/550,325, filed on Aug. 25, 2017, provisional application No. 62/550,307, filed on Aug. 25, 2017, provisional application No. 62/529,515, filed on Jul. 7, 2017, provisional application No. 62/523,458, filed on Jun. 22, 2017.

Publication Classification

(51) **Int. Cl.**

C07K 16/24	(2006.01)
A61P 35/00	(2006.01)
G01N 33/574	(2006.01)
A61K 9/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/245*** (2013.01); ***A61P 35/00*** (2018.01); *A61K 31/282* (2013.01); ***A61K 9/0019*** (2013.01); *A61K 2300/00* (2013.01); ***G01N 33/57423*** (2013.01)

(57) **ABSTRACT**

Use of an IL-1β binding antibody or a functional fragment thereof, especially canakinumab or a functional fragment thereof, or gevokizumab or a functional fragment thereof, and biomarkers for the treatment and/or prevention of cancer with at least partial inflammatory basis.

Specification includes a Sequence Listing.

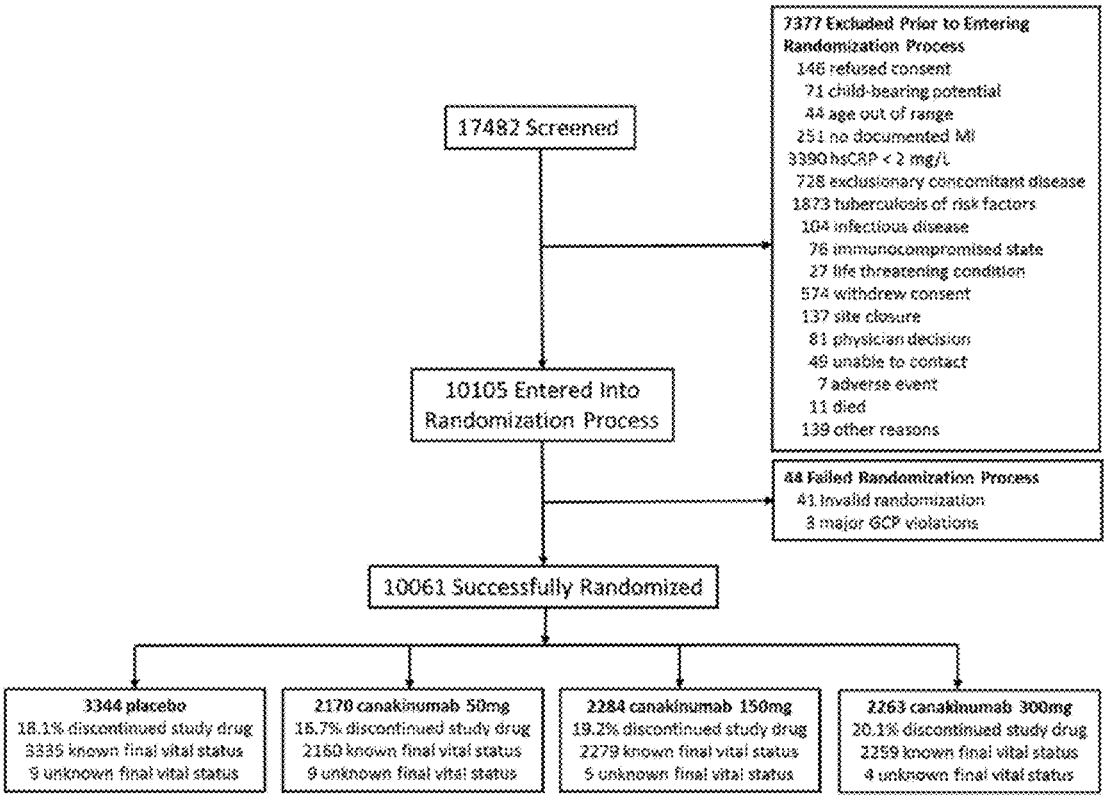


FIG. 1

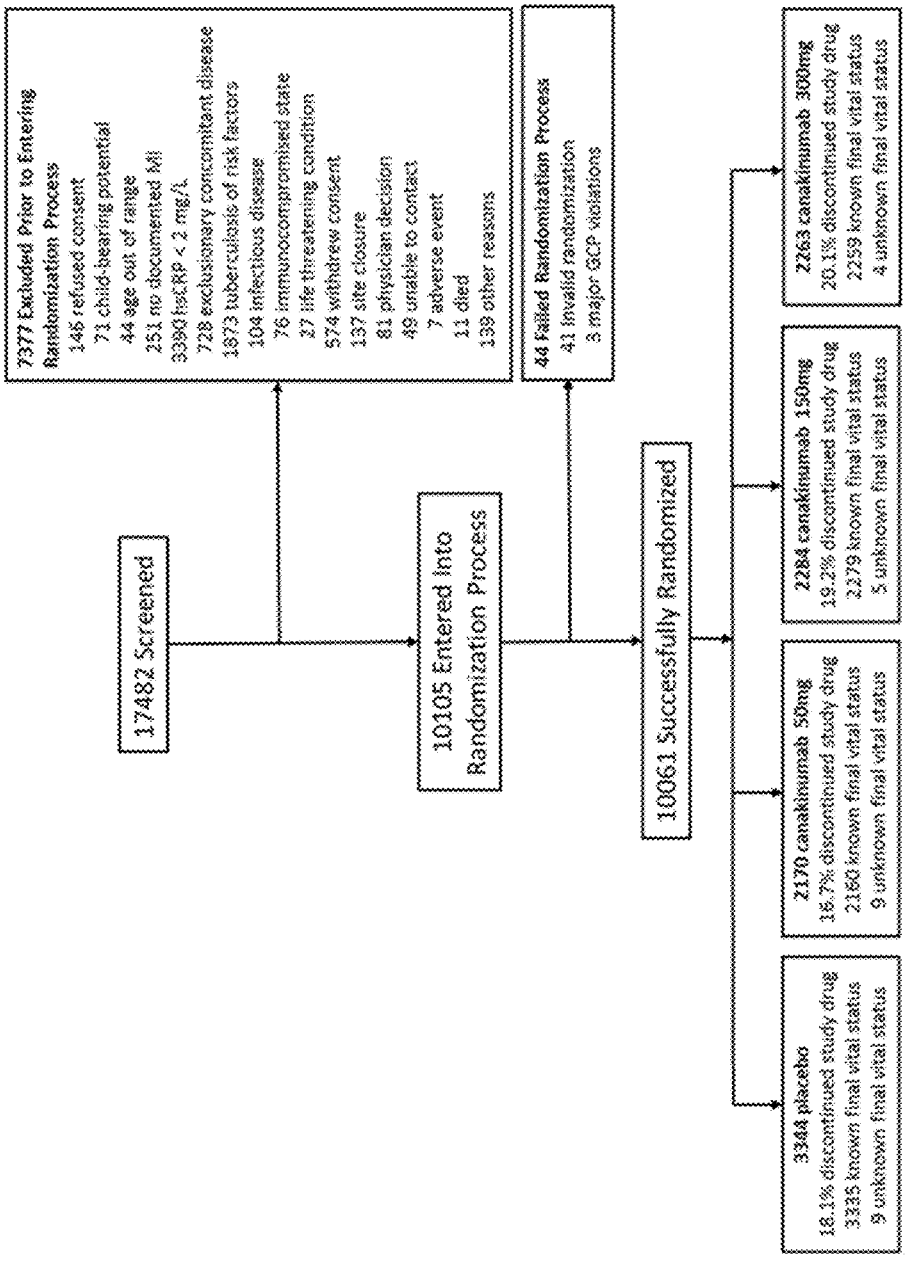

17482 Screened
7377 Excluded Prior to Entering Randomization Process
146 refused consent
71 child-bearing potential
44 age out of range
251 no documented MI
3390 hsCRP < 2 mg/L
728 exclusionary concomitant disease
1873 tuberculosis of risk factors
104 infectious disease
76 immunocompromised state
37 life threatening condition
574 withdrew consent
137 site closure
81 physician decision
49 unable to contact
7 adverse event
11 died
139 other reasons
10105 Entered into Randomization Process
44 Failed Randomization Process
41 invalid randomization
3 major GCP violations
10061 Successfully Randomized
3344 placebo
16.1% discontinued study drug
3335 known final vital status
9 unknown final vital status
2170 canakinumab 50mg
16.7% discontinued study drug
2160 known final vital status
9 unknown final vital status
2284 canakinumab 150mg
19.2% discontinued study drug
2279 known final vital status
5 unknown final vital status
2263 canakinumab 300mg
20.1% discontinued study drug
2259 known final vital status
4 unknown final vital status

FIG. 2

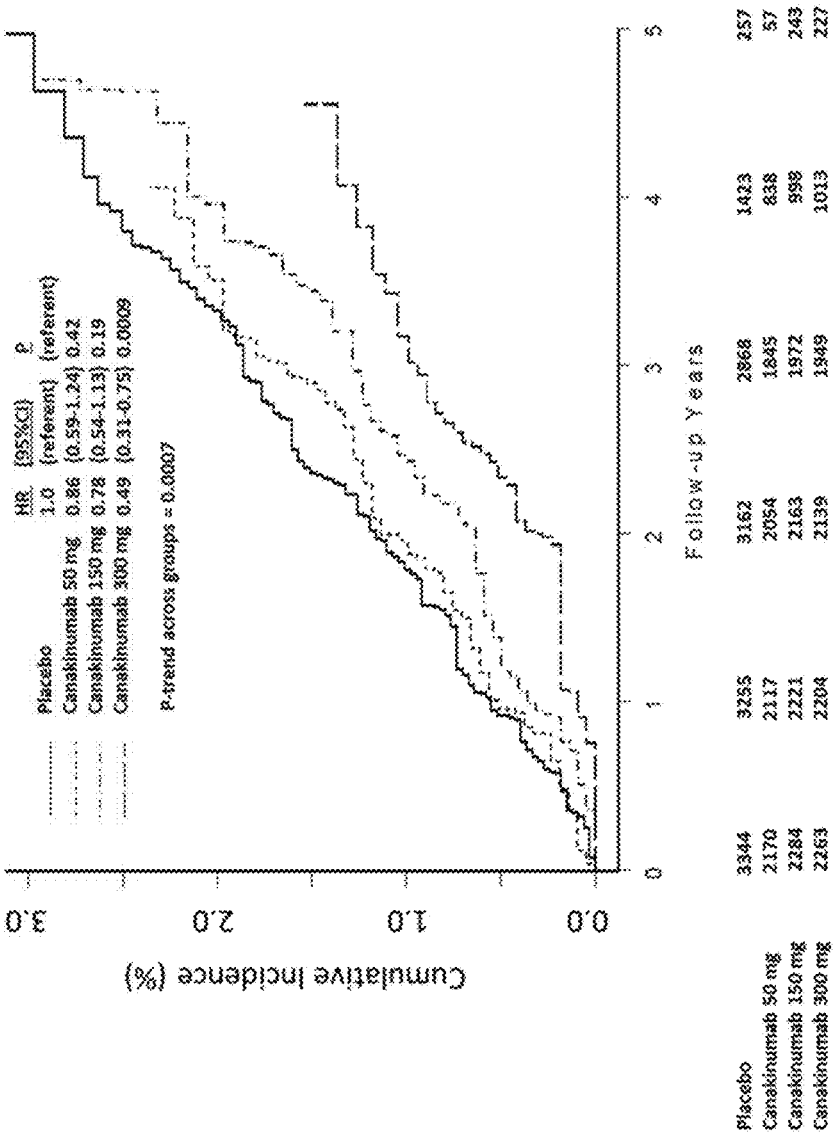

All Fatal Cancer
HR (95%CI) p
Placebo 1.0 (referent) (referent)
Canakinumab 50 mg 0.86 (0.59-1.24) 0.42
Canakinumab 150 mg 0.78 (0.54-1.13) 0.19
Canakinumab 300 mg 0.49 (0.31-0.75) 0.0009
P-trend across groups = 0.0007
Cumulative Incidence (%)
0.0
1.0
2.0
3.0
0
1
2
3
4
5
Follow-up Years
Placebo 3344 3255 3162 2868 1423 257
Canakinumab 50 mg 2170 2117 2054 1845 838 57
Canakinumab 150 mg 2284 2221 2163 1972 998 243
Canakinumab 300 mg 2263 2204 2139 1949 1013 227

FIG. 3

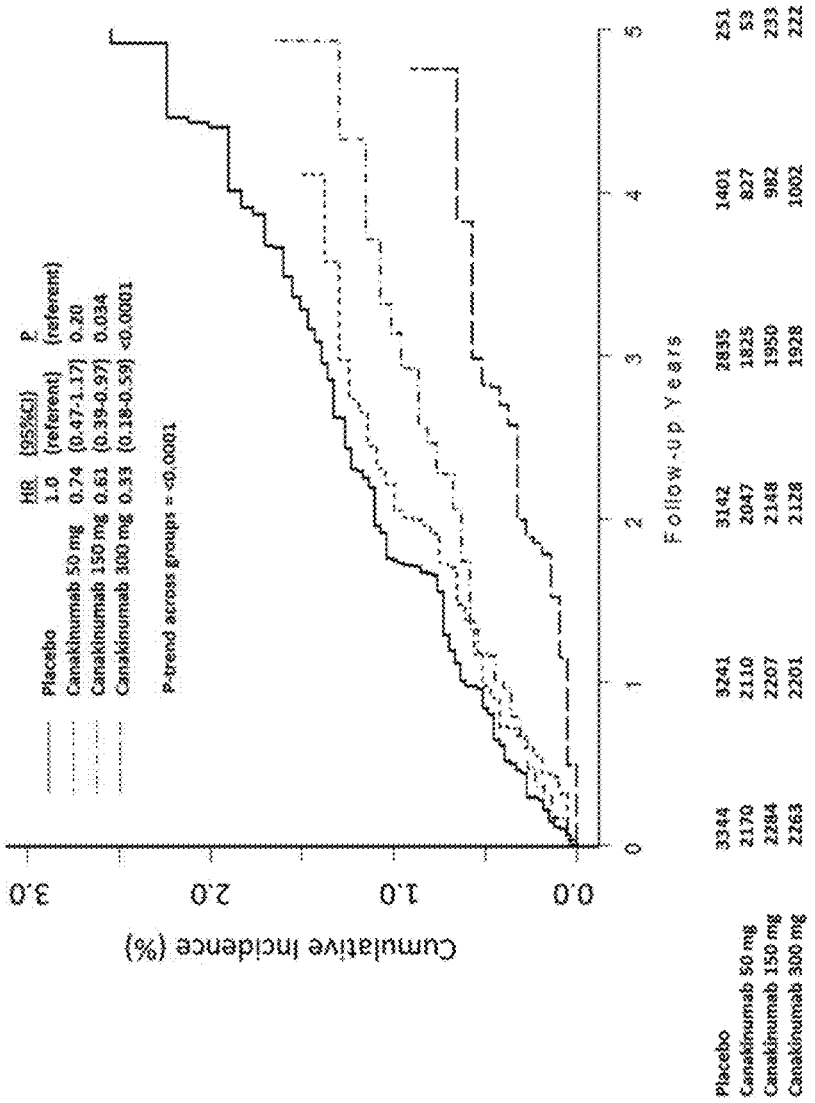

Lung Cancer
HR (95%CI) P
Placebo 1.0 (referent) (referent)
Canakinumab 50 mg 0.74 (0.47-1.17) 0.20
Canakinumab 150 mg 0.61 (0.39-0.97) 0.034
Canakinumab 300 mg 0.33 (0.18-0.59) <0.0001
P-trend across groups = <0.0001
Cumulative Incidence (%)
0.0
1.0
2.0
3.0
0
1
2
3
4
5
Follow-up Years
Placebo 3344 3241 3142 2935 1401 251
Canakinumab 50 mg 2170 2110 2047 1825 827 53
Canakinumab 150 mg 2284 2207 2148 1950 982 233
Canakinumab 300 mg 2263 2201 2128 1928 1002 222

FIG. 4

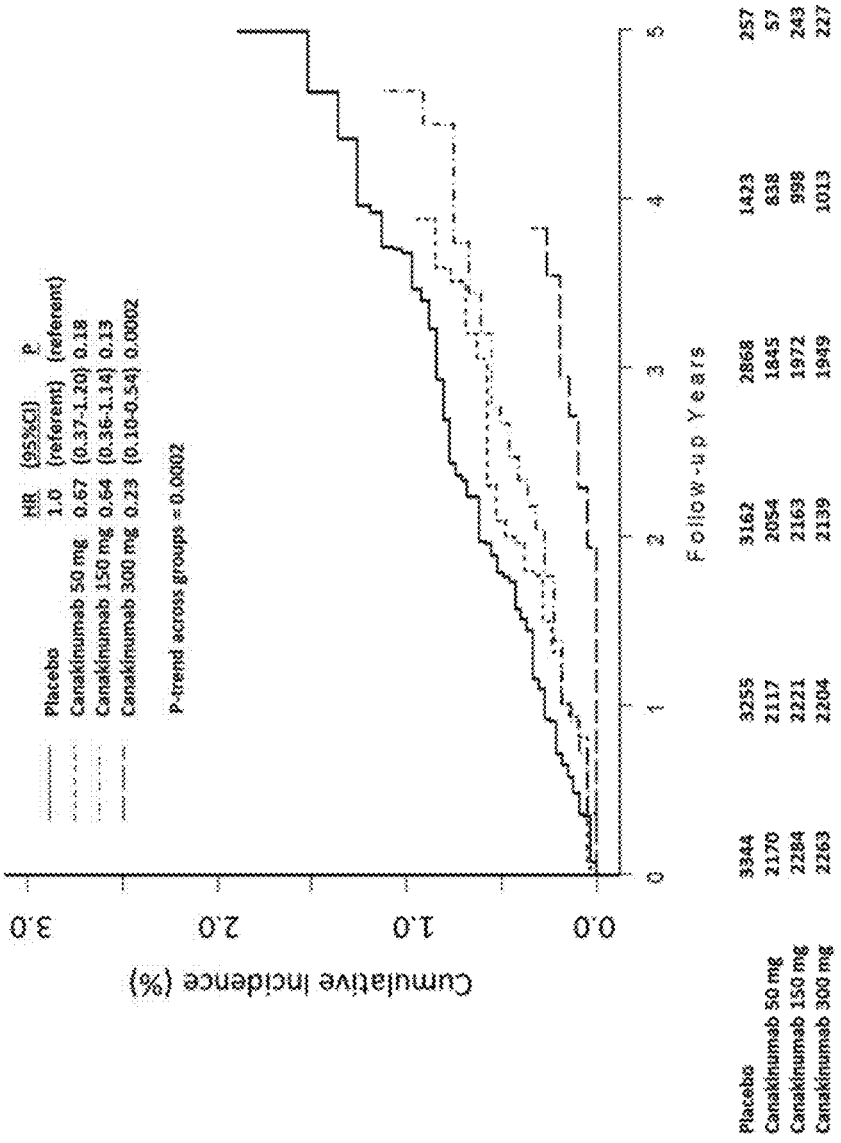

Fatal Lung Cancer
HR (95%CI) p
Placebo 1.0 (referent) (referent)
Canakinumab 50 mg 0.67 (0.37-1.20) 0.18
Canakinumab 150 mg 0.64 (0.36-1.14) 0.13
Canakinumab 300 mg 0.23 (0.10-0.54) 0.0002
P-trend across groups = 0.0002
Cumulative Incidence (%)
0.0
1.0
2.0
3.0
0
1
2
3
4
5
Follow-up Years
Placebo 3344 3255 3162 2868 1423 257
Canakinumab 50 mg 2170 2117 2054 1845 838 57
Canakinumab 150 mg 2284 2221 2163 1972 998 243
Canakinumab 300 mg 2263 2204 2139 1949 1013 227

FIG. 5

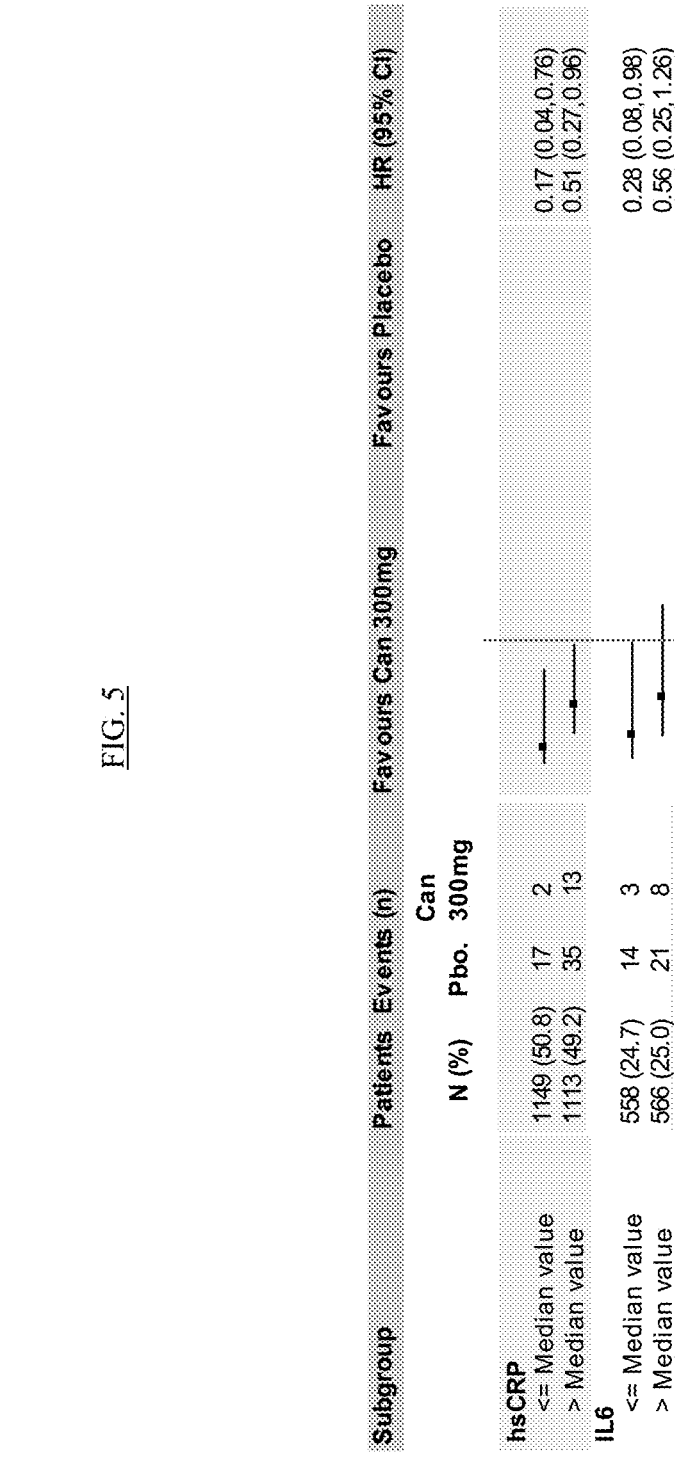

Subgroup
Patients
Events (n)
Favours Can 300mg
Favours Placebo
HR (95% CI)
Can
N (%)
Pbo.
300mg
hsCRP
<= Median value
1149 (50.8)
17
2
0.17 (0.04,0.76)
> Median value
1113 (49.2)
35
13
0.51 (0.27,0.96)
IL6
<= Median value
558 (24.7)
14
3
0.28 (0.08,0.98)
> Median value
566 (25.0)
21
8
0.56 (0.25,1.26)

FIG. 6

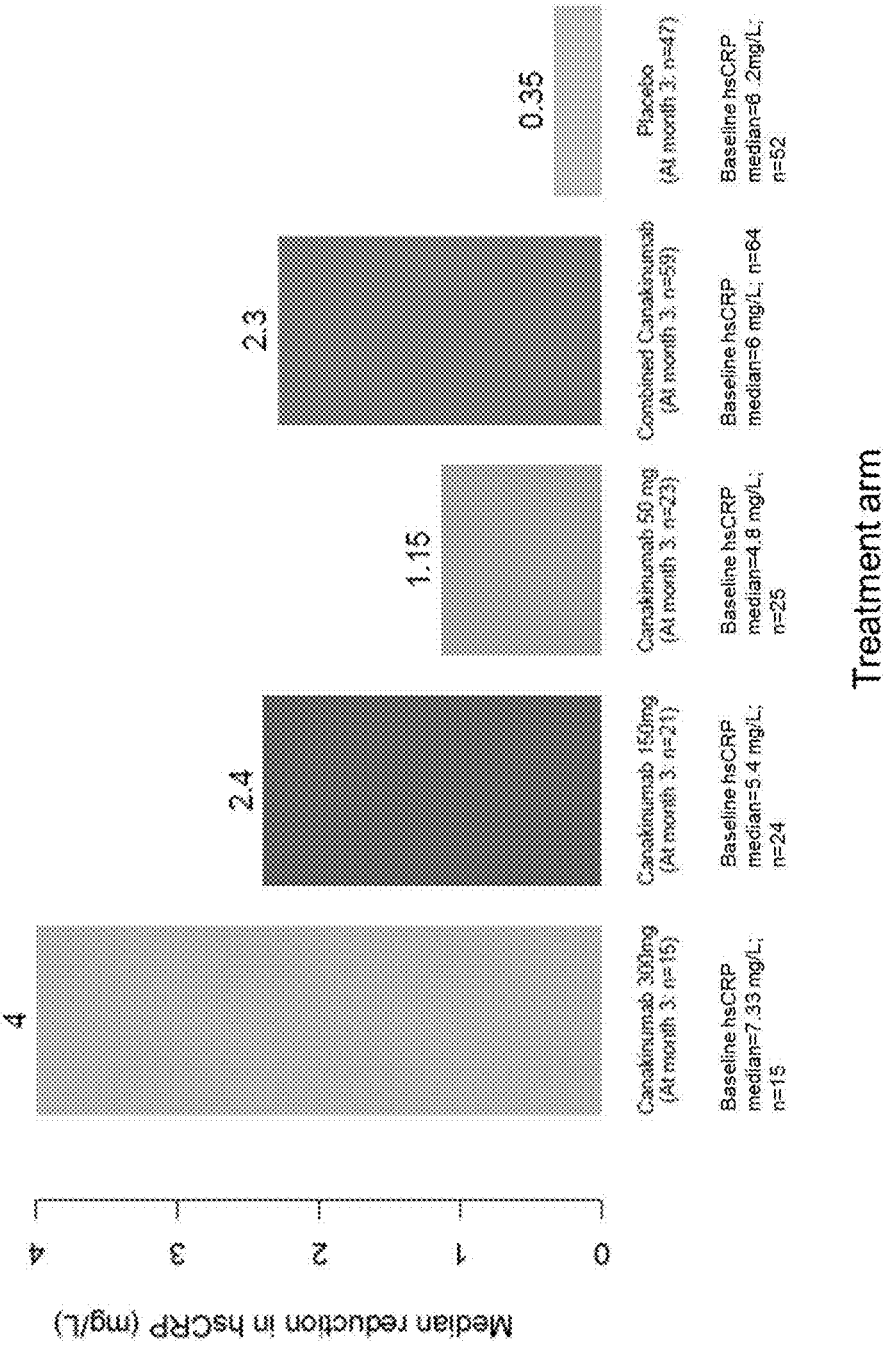

Median reduction in hsCRP (mg/L)
0
1
2
3
4
4
2.4
1.15
2.3
0.35
Canakinumab 300mg (At month 3, n=15)
Canakinumab 150mg (At month 3, n=21)
Canakinumab 50 mg (At month 3, n=23)
Combined Canakinumab (At month 3, n=59)
Placebo (At month 3, n=47)
Baseline hsCRP median=7.33 mg/L; n=15
Baseline hsCRP median=5.4 mg/L; n=24
Baseline hsCRP median=4.8 mg/L; n=25
Baseline hsCRP median=6 mg/L; n=64
Baseline hsCRP median=6 .2mg/L; n=52
Treatment arm

FIG. 7

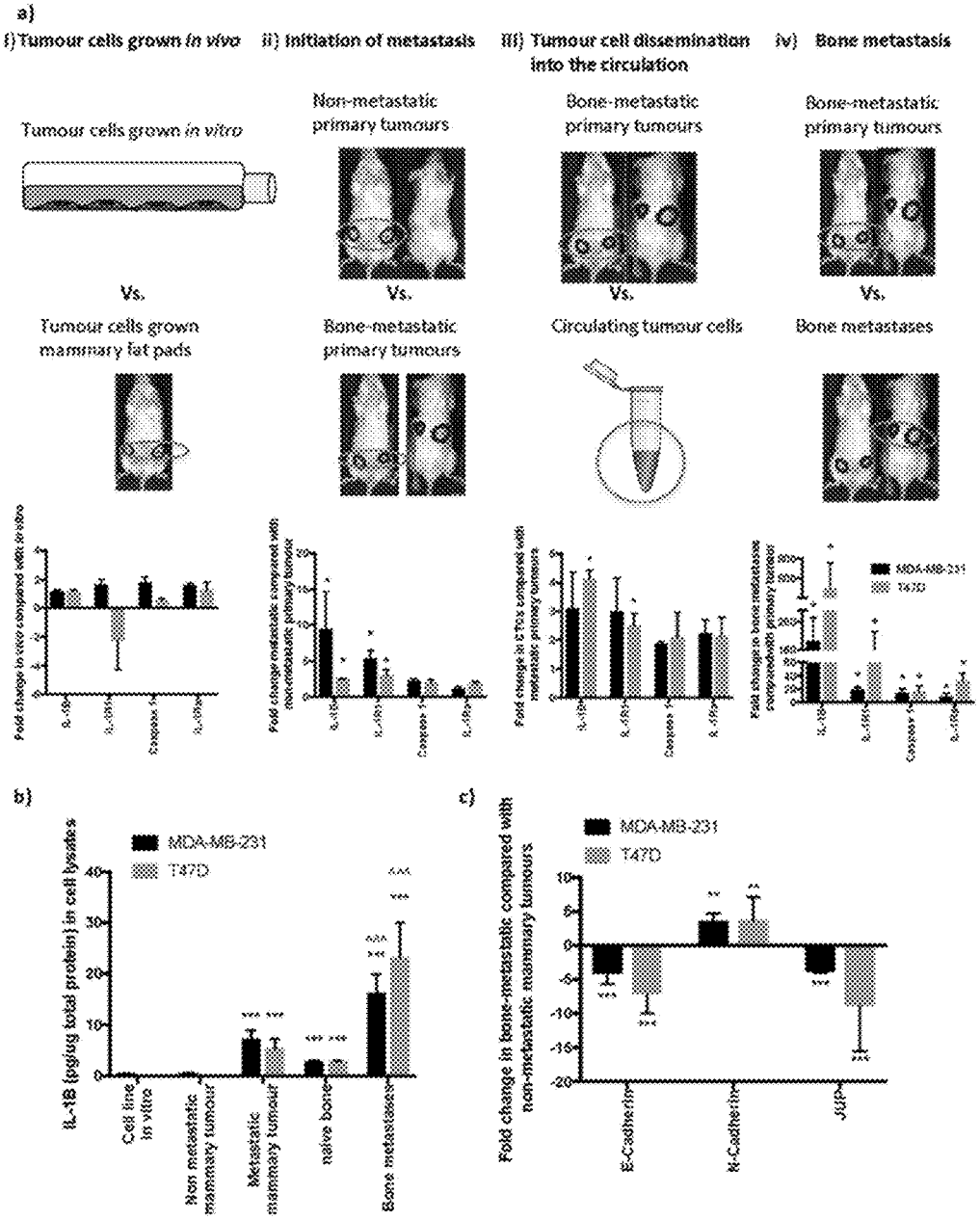

a)
i) Tumour cells grown in vivo
ii) Initiation of metastasis
iii) Tumour cell dissemination into the circulation
iv) Bone metastasis
Tumour cells grown in vitro
Non-metastatic primary tumours
Bone-metastatic primary tumours
Bone-metastatic primary tumours
Vs.
Vs.
Vs.
Vs.
Tumour cells grown mammary fat pads
Bone-metastatic primary tumours
Circulating tumour cells
Bone metastases
b)
IL-1B (pg/ug total protein) in cell lysates
MDA-MB-231
T47D
Cell line in vitro
Non metastatic mammary tumour
Metastatic mammary tumour
naive bone
Bone metastases
c)
Fold change in bone-metastatic compared with non-metastatic mammary tumours
MDA-MB-231
T47D
E-Cadherin
N-Cadherin
JUP

FIG. 8

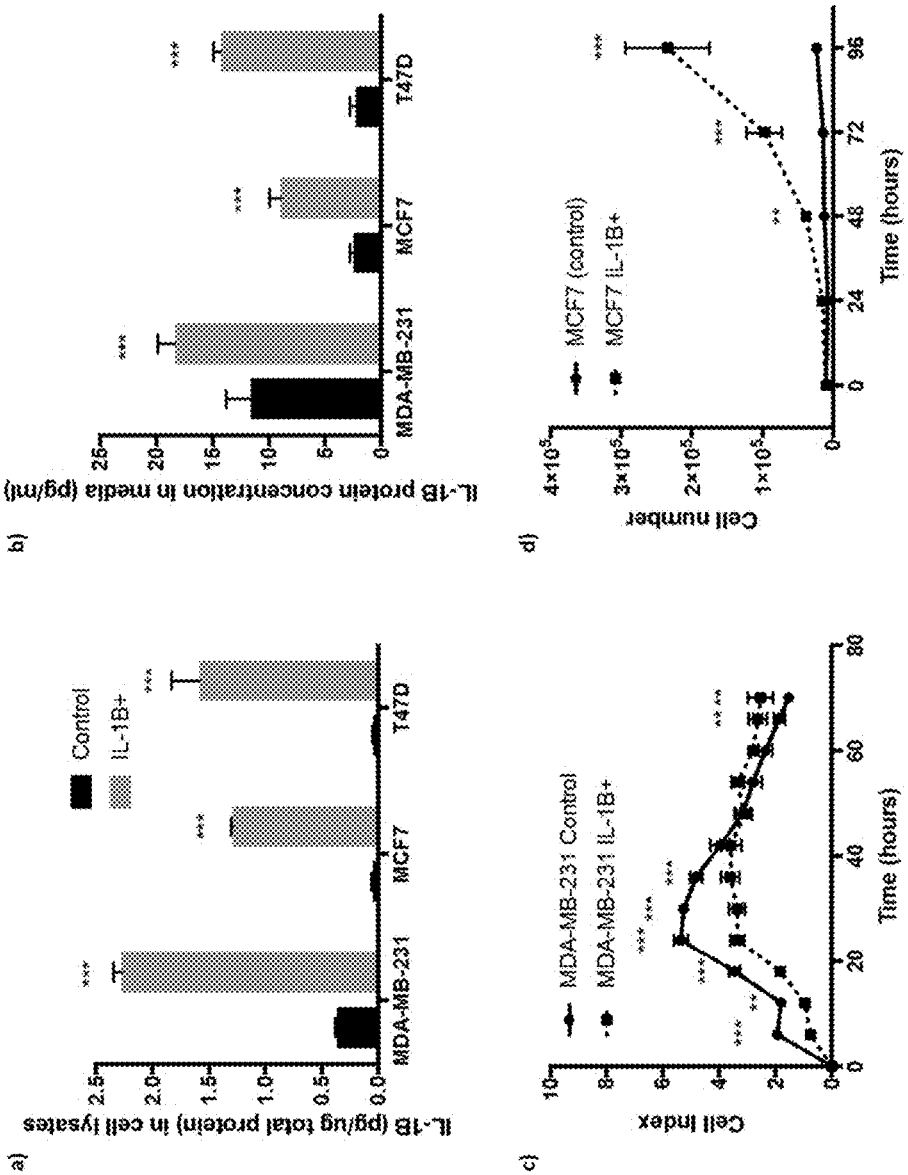

a)
IL-1B (pg/ug total protein) in cell lysates
Control
IL-1B+
MDA-MB-231
MCF7
T47D
b)
IL-1B protein concentration in media (pg/ml)
c)
Cell Index
MDA-MB-231 Control
MDA-MB-231 IL-1B+
Time (hours)
d)
Cell number
MCF7 (control)
MCF7 IL-1B+
Time (hours)

FIG. 9

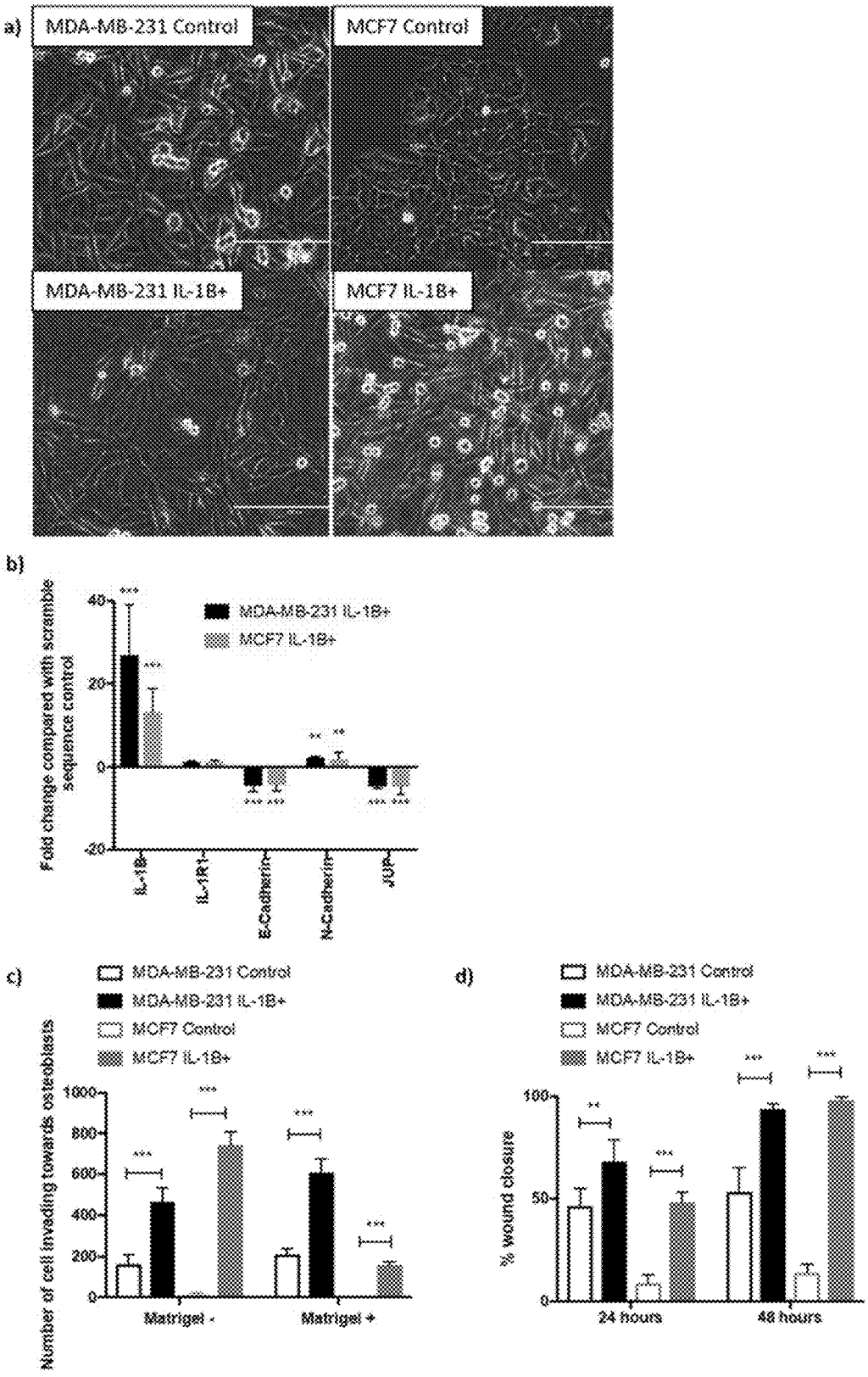

a)
MDA-MB-231 Control
MCF7 Control
MDA-MB-231 IL-1B+
MCF7 IL-1B+
b)
MDA-MB-231 IL-1B+
MCF7 IL-1B+
Fold change compared with scramble sequence control
IL-1B
IL-1R1
E-Cadherin
N-Cadherin
JUP
c)
MDA-MB-231 Control
MDA-MB-231 IL-1B+
MCF7 Control
MCF7 IL-1B+
Number of cell invading towards osteoblasts
Matrigel -
Matrigel +
d)
MDA-MB-231 Control
MDA-MB-231 IL-1B+
MCF7 Control
MCF7 IL-1B+
% wound closure
24 hours
48 hours

FIG. 10

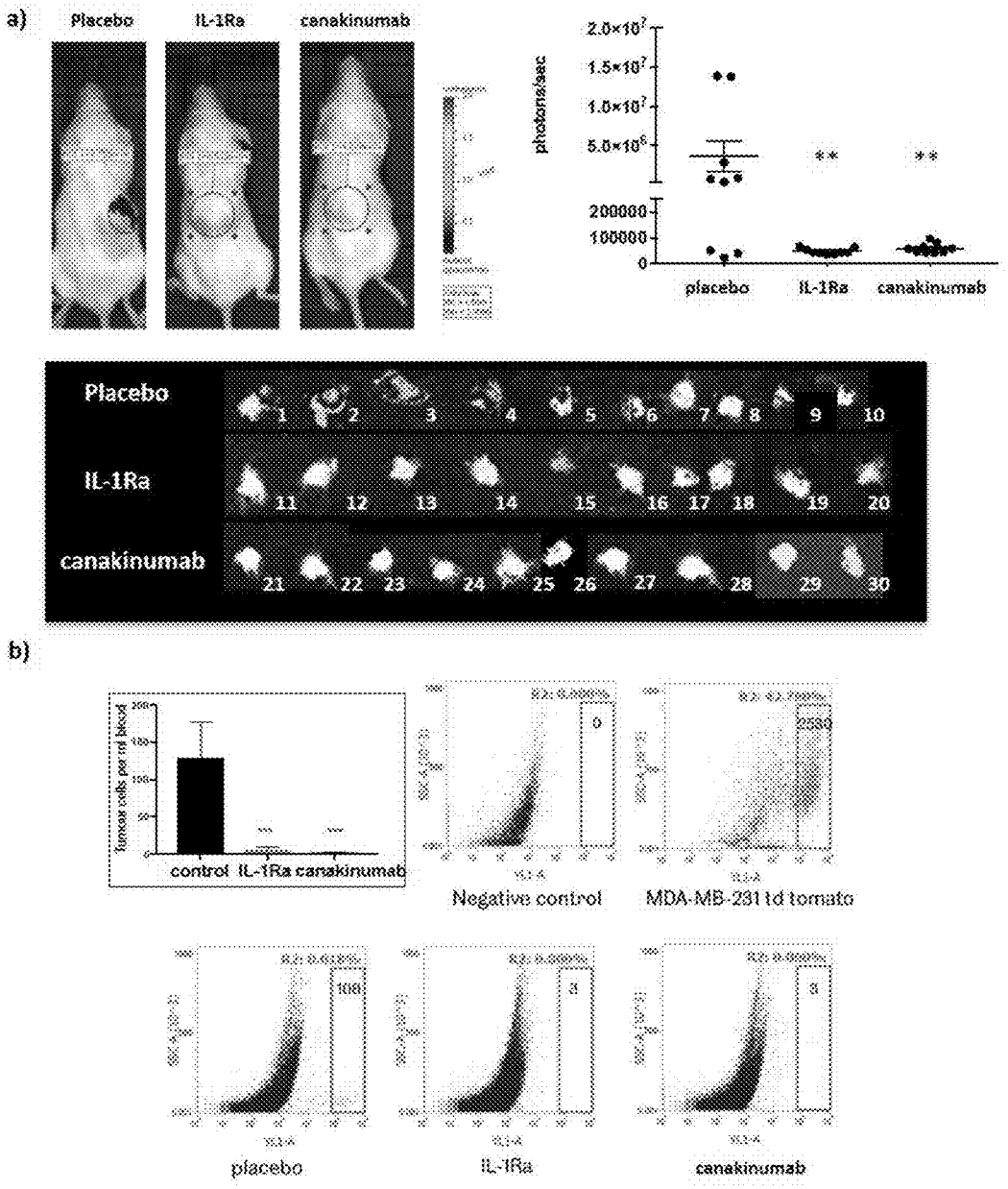

a)
Placebo
IL-1Ra
canakinumab
photons/sec
placebo
IL-1Ra
canakinumab
Placebo
IL-1Ra
canakinumab
b)
Tumor cells per ml blood
control
IL-1Ra
canakinumab
Negative control
MDA-MB-231 td tomato
placebo
IL-1Ra
canakinumab

FIG. 11

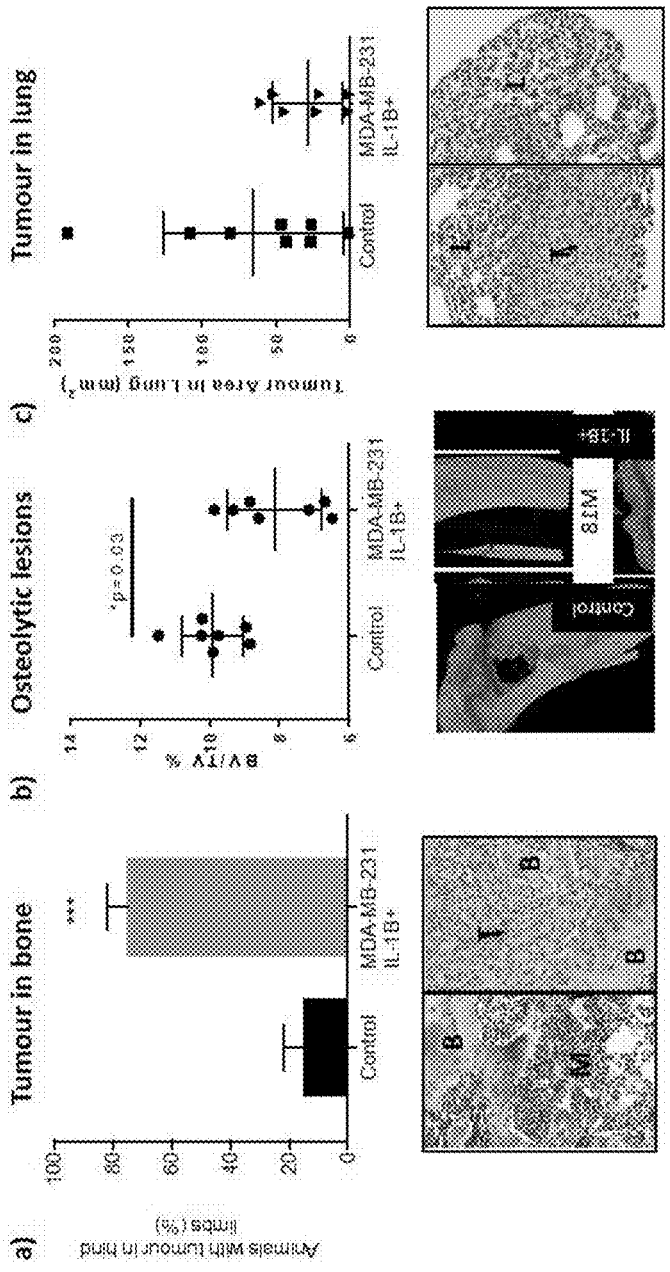

a)
Animals with tumour in hind limbs (%)
Tumour in bone
***
Control
MDA-MB-231 IL-1B+
b)
BV/TV %
Osteolytic lesions
*p=0.03
Control
MDA-MB-231 IL-1B+
c)
Tumour Area in Lung (mm²)
Tumour in lung
Control
MDA-MB-231 IL-1B+
B
T
M
Control
MIB
IL-1B+
L
T

FIG. 12

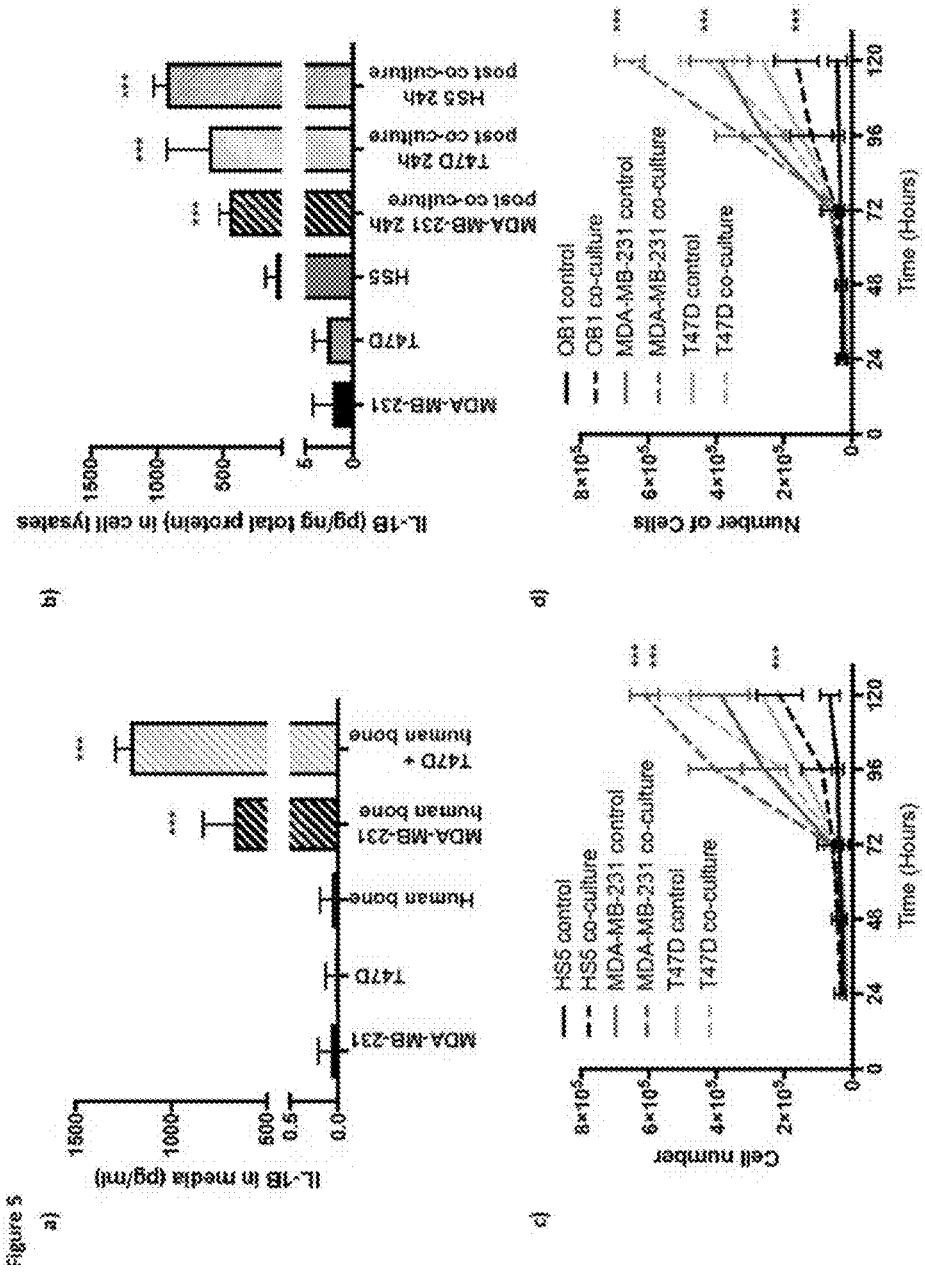


Figure 5
a)
IL-1B in media (pg/ml)
1500
1000
500
0.5
0.0
MDA-MB-231
T47D
Human bone
MDA-MB-231 human bone
T47D + human bone
***
b)
IL-1B (pg/ng total protein) in cell lysates
1500
1000
500
5
0
MDA-MB-231
T47D
HS5
MDA-MB-231 24h post co-culture
T47D 24h post co-culture
HS5 24h post co-culture
***
c)
Cell number
8×10^5
6×10^5
4×10^5
2×10^5
0
24
48
72
96
120
Time (Hours)
HS5 control
HS5 co-culture
MDA-MB-231 control
MDA-MB-231 co-culture
T47D control
T47D co-culture
***
d)
Number of Cells
8×10^5
6×10^5
4×10^5
2×10^5
0
24
48
72
96
120
Time (Hours)
OB1 control
OB1 co-culture
MDA-MB-231 control
MDA-MB-231 co-culture
T47D control
T47D co-culture
***

FIG. 13

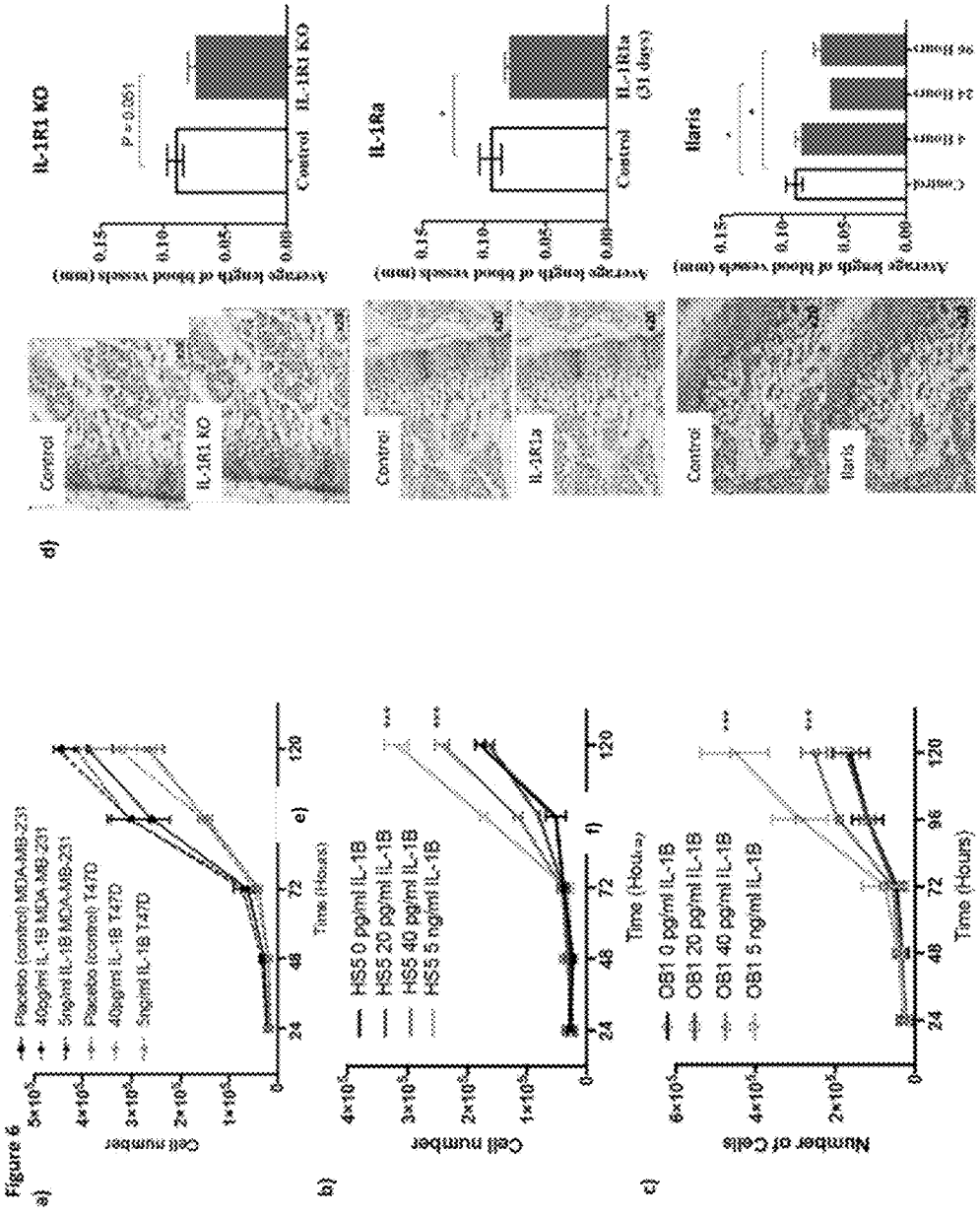


Figure 6
a)
Placebo (control) MDA-MB-231
40pg/ml IL-1B MDA-MB-231
5ng/ml IL-1B MDA-MB-231
Placebo (control) T47D
40pg/ml IL-1B T47D
5ng/ml IL-1B T47D
Cell number
Time (Hours)
b)
HS5 0 pg/ml IL-1B
HS5 20 pg/ml IL-1B
HS5 40 pg/ml IL-1B
HS5 5 ng/ml IL-1B
Cell number
Time (Hours)
c)
OB1 0 pg/ml IL-1B
OB1 20 pg/ml IL-1B
OB1 40 pg/ml IL-1B
OB1 5 ng/ml IL-1B
Number of Cells
Time (Hours)
d)
IL-1R1 KO
Control
IL-1R1 KO
Average length of blood vessels (mm)
P = 0.051
IL-1Ra
Control
IL-1Ra (31 days)
Average length of blood vessels (mm)
Ilaris
Control
Ilaris
Average length of blood vessels (mm)
control
4 hours
24 hours
96 hours

FIG. 14

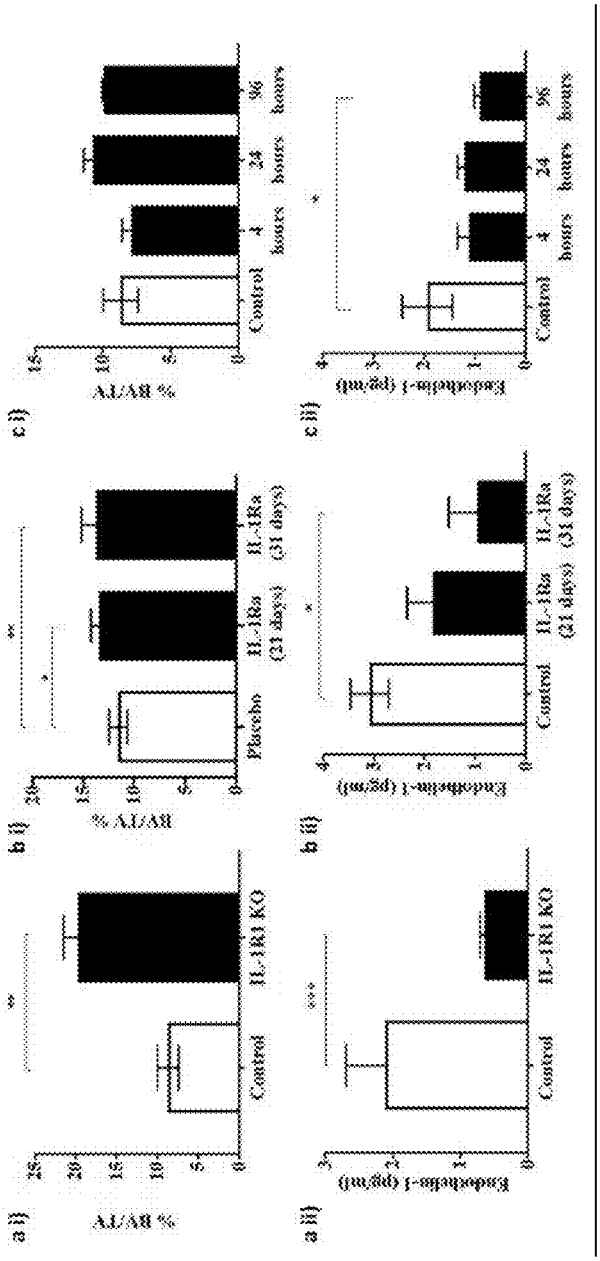

a i)
AL/AB %
Control
IL-1R1 KO
a ii)
Endothelin-1 (pg/ml)
Control
IL-1R1 KO
b i)
% AL/AB
Placebo
IL-1Ra (21 days)
IL-1Ra (31 days)
b ii)
Endothelin-1 (pg/ml)
Control
IL-1Ra (21 days)
IL-1Ra (31 days)
c i)
AL/AB %
Control
4 hours
24 hours
96 hours
c ii)
Endothelin-1 (pg/ml)
Control
4 hours
24 hours
96 hours

FIG. 15

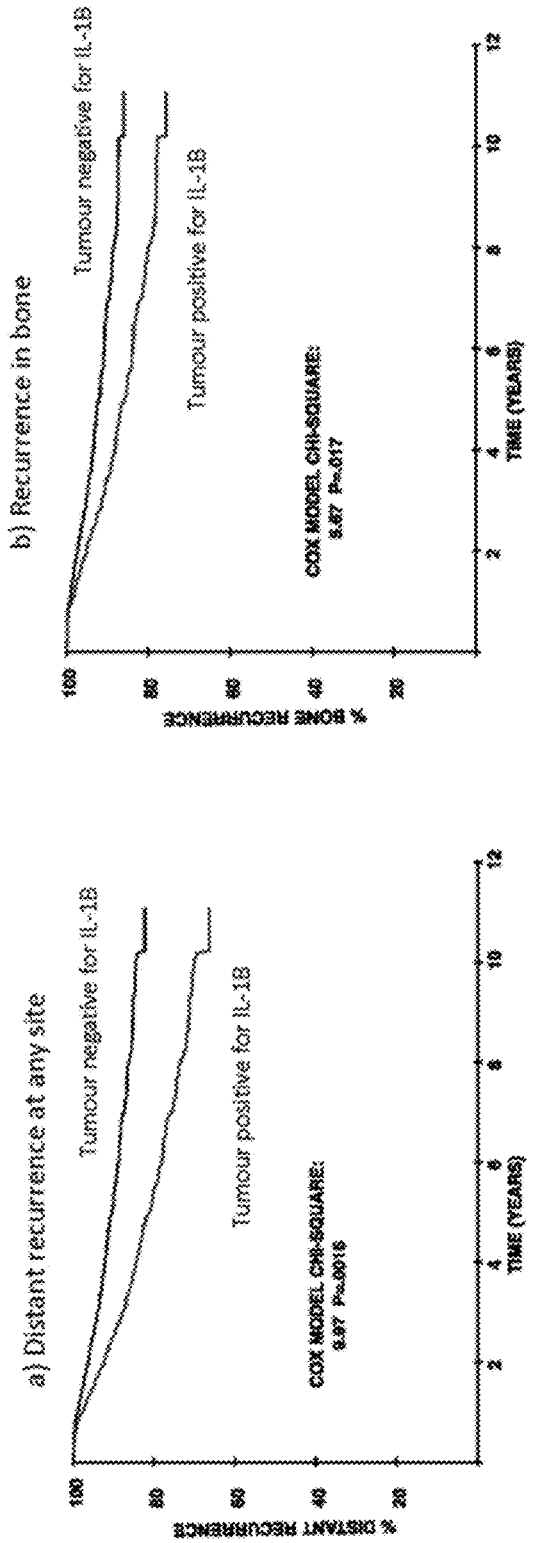
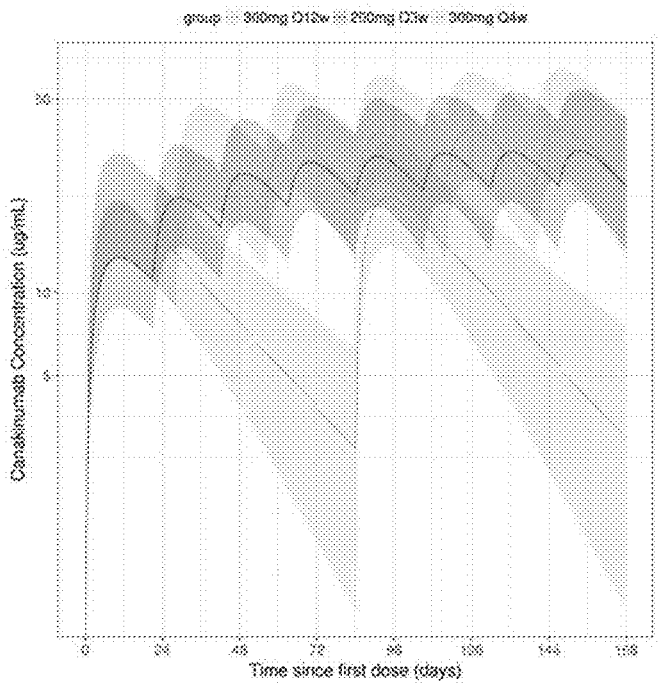

a) Distant recurrence at any site
Tumour negative for IL-1B
Tumour positive for IL-1B
COX MODEL CHI-SQUARE:
% DISTANT RECURRENCE
TIME (YEARS)
b) Recurrence in bone
Tumour negative for IL-1B
Tumour positive for IL-1B
COX MODEL CHI-SQUARE:
% BONE RECURRENCE
TIME (YEARS)

FIG. 16

a)


group 300mg Q12w 250mg Q3w 300mg Q4w
Canakinumab Concentration (ug/mL)
Time since first dose (days)

b)

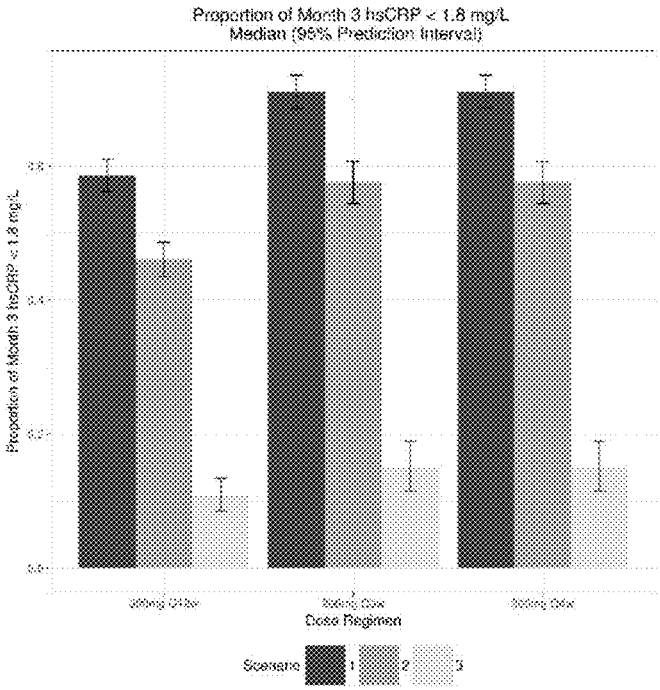
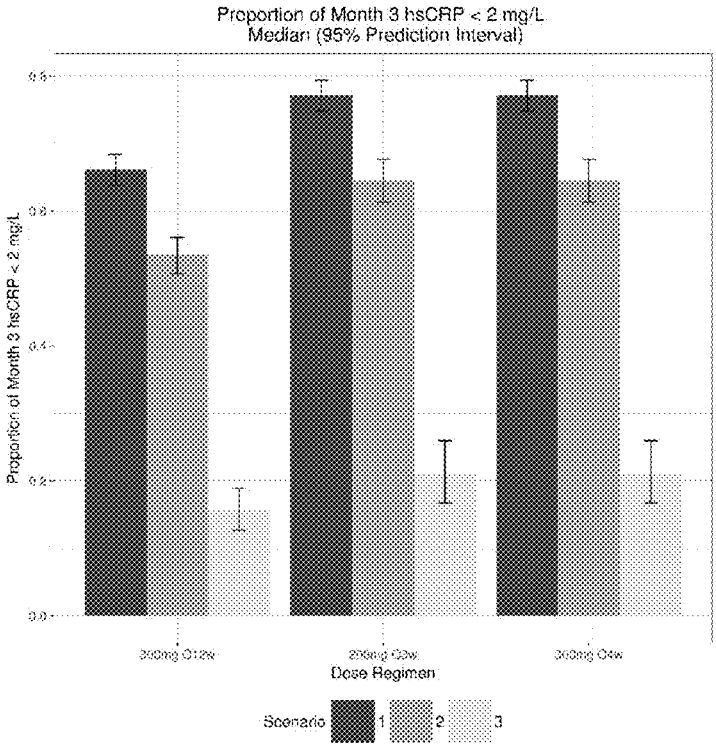

Proportion of Month 3 hsCRP < 1.8 mg/L
Median (95% Prediction Interval)
Proportion of Month 3 hsCRP < 1.8 mg/L
Dose Regimen
Scenario 1 2 3

FIG. 16 (cont.)

c)



d)

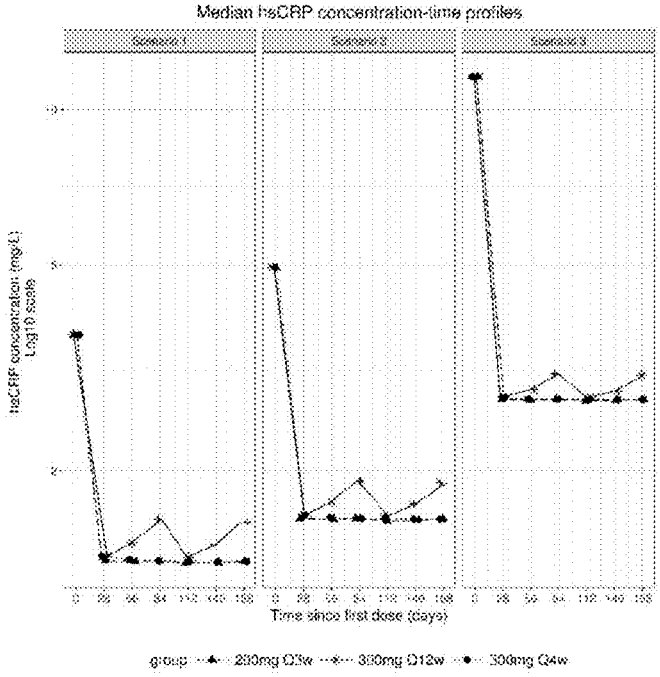


FIG. 16 (cont.)

e)

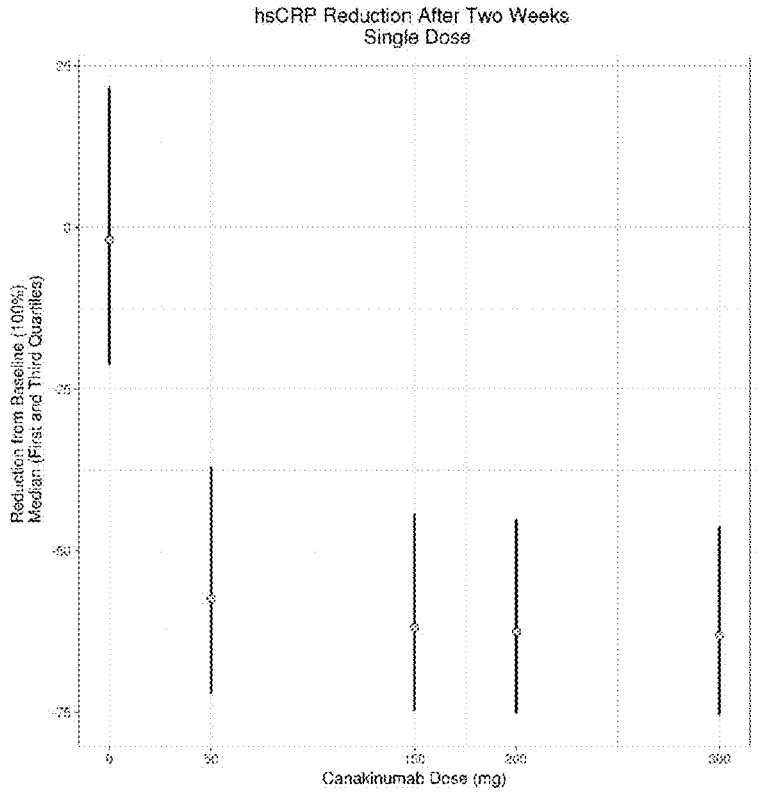

hsCRP Reduction After Two Weeks
Single Dose
Reduction from Baseline (100%)
Median (First and Third Quartiles)
Canakinumab Dose (mg)

FIG. 17

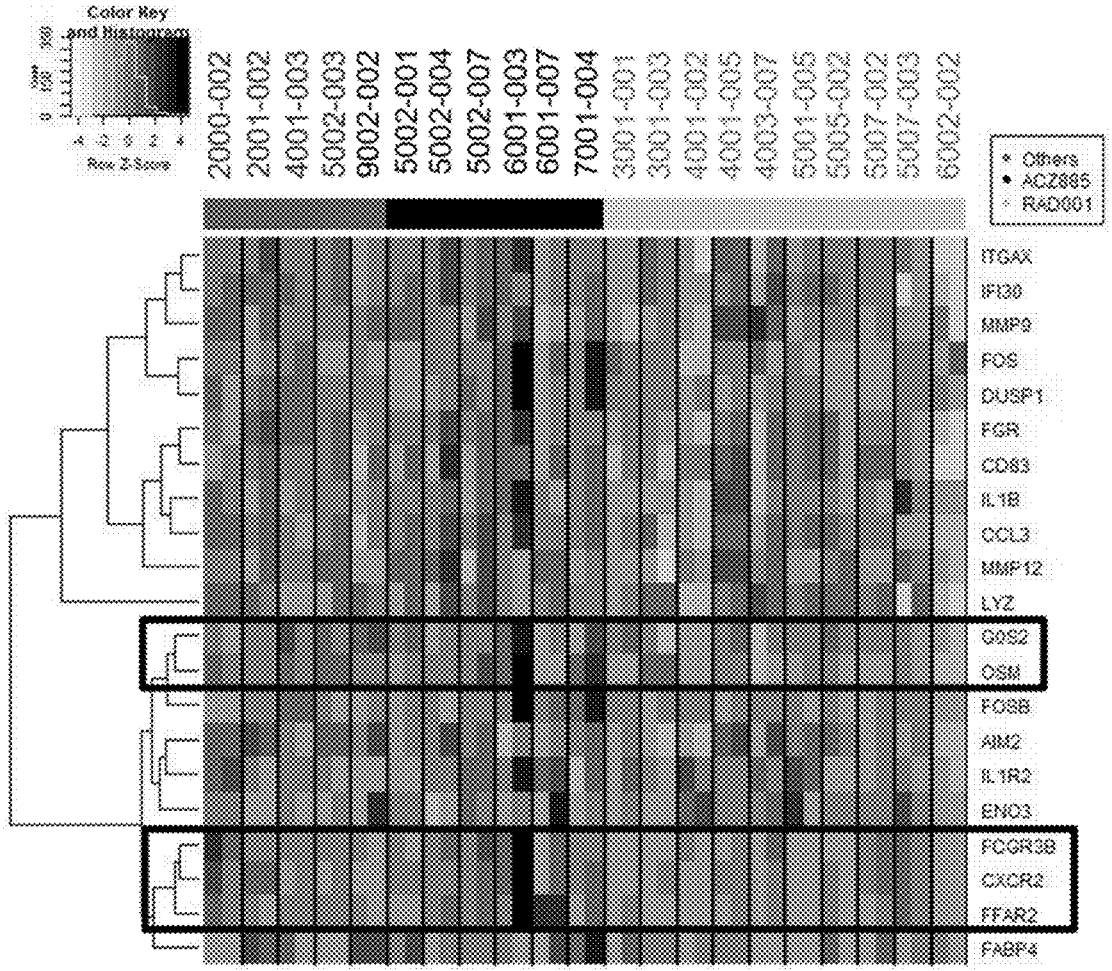
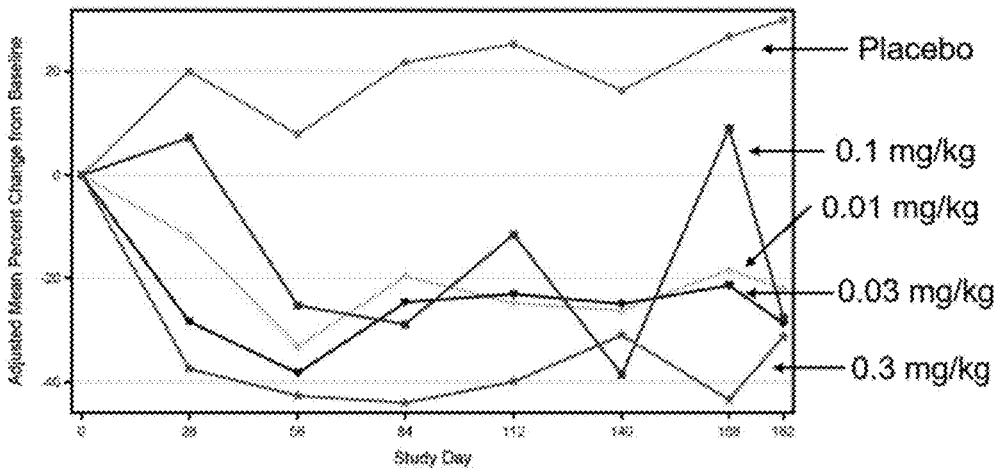

Color Key and Histogram
Count
Row Z-Score
2000-002
2001-002
4001-003
5002-003
9002-002
5002-001
5002-004
5002-007
6001-003
6001-007
7001-004
3001-001
3001-003
4001-002
4001-005
4003-007
5001-005
5005-002
5007-002
5007-003
6002-002
Others
ACZ885
RAD001
ITGAX
IFI30
MMP9
FOS
DUSP1
FGR
CD83
IL1B
CCL3
MMP12
LYZ
G0S2
OSM
FOSB
AIM2
IL1R2
ENO3
FCGR3B
CXCR2
FFAR2
FABP4

FIG. 18

a)


Placebo
0.1 mg/kg
0.01 mg/kg
0.03 mg/kg
0.3 mg/kg
Adjusted Mean Percent Change from Baseline
Study Day

b)

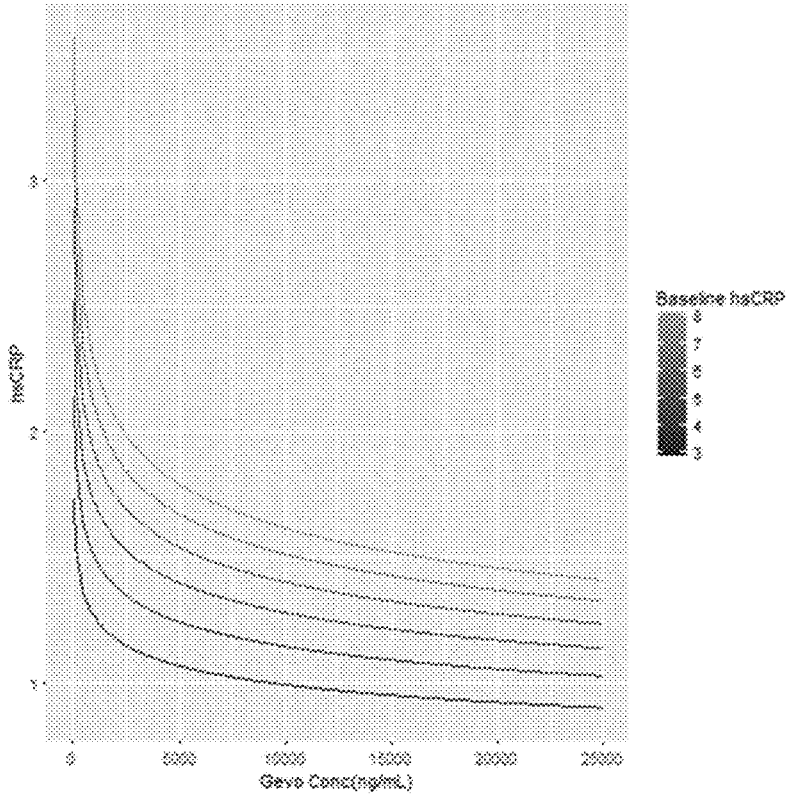
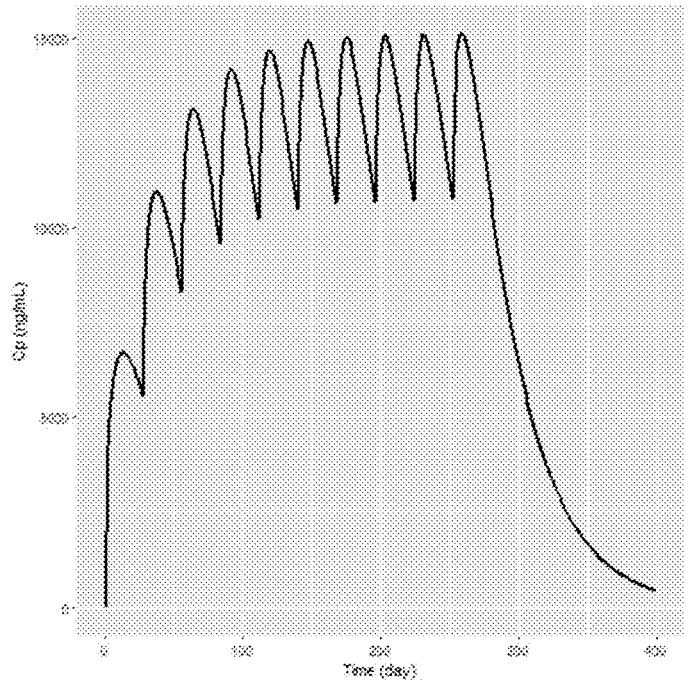

Baseline hsCRP
hsCRP
Gevo Conc(ng/mL)

FIG. 18 (cont.)

c)



d)

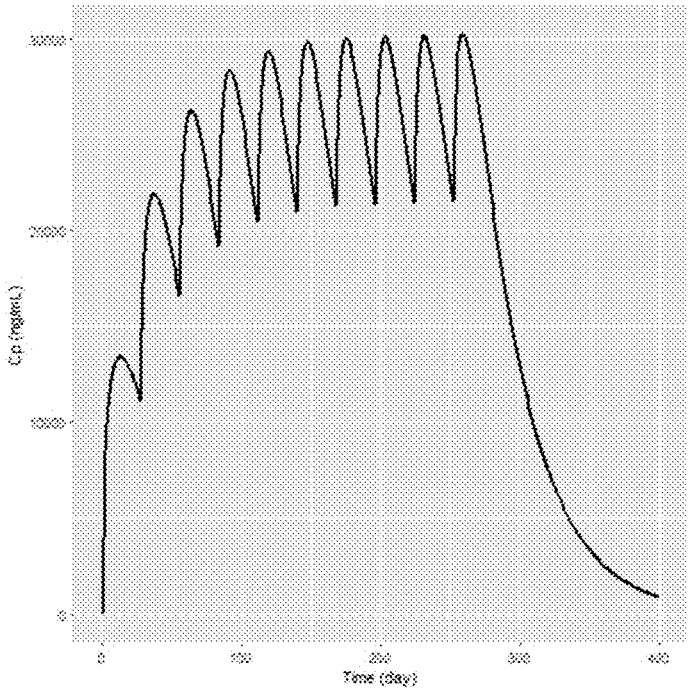


FIG. 19

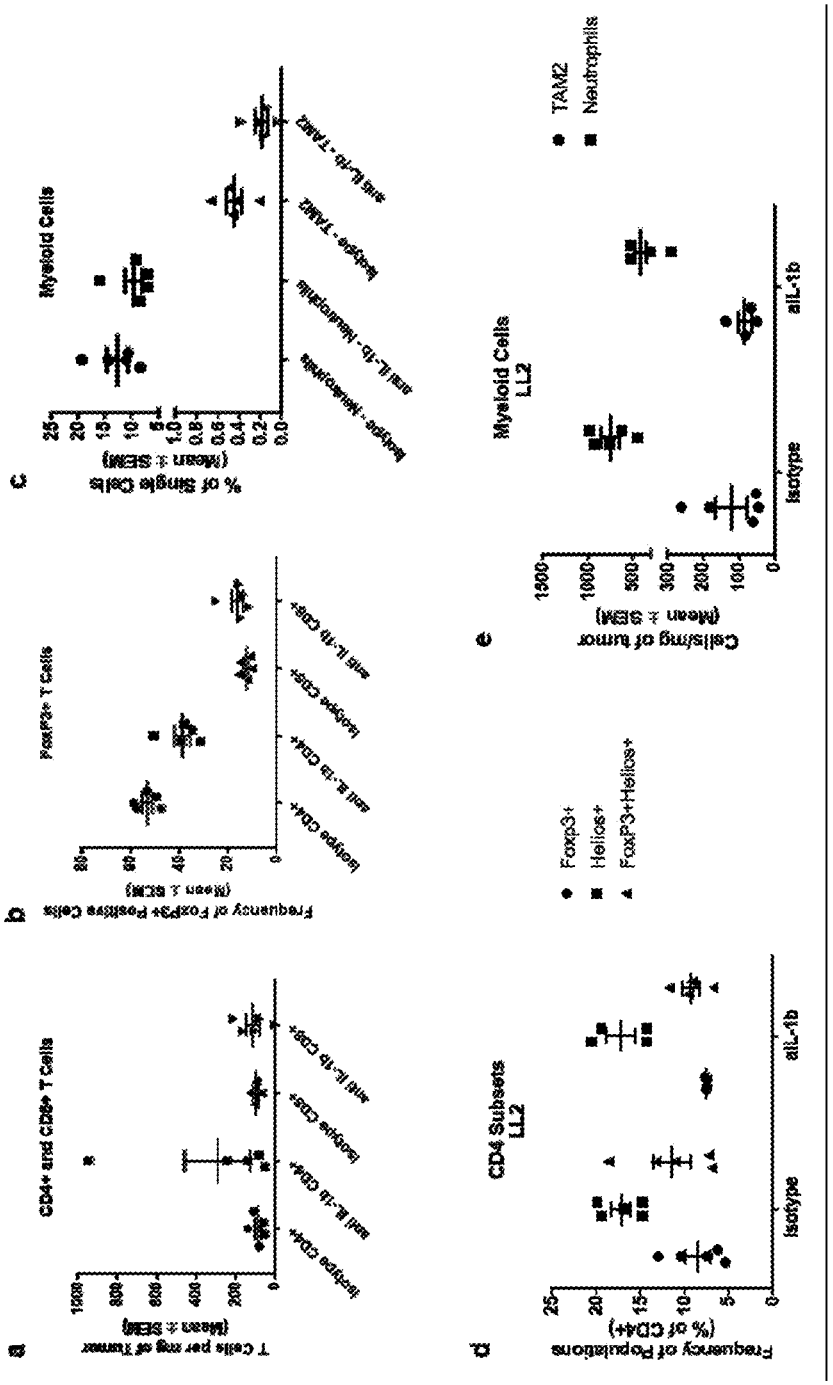
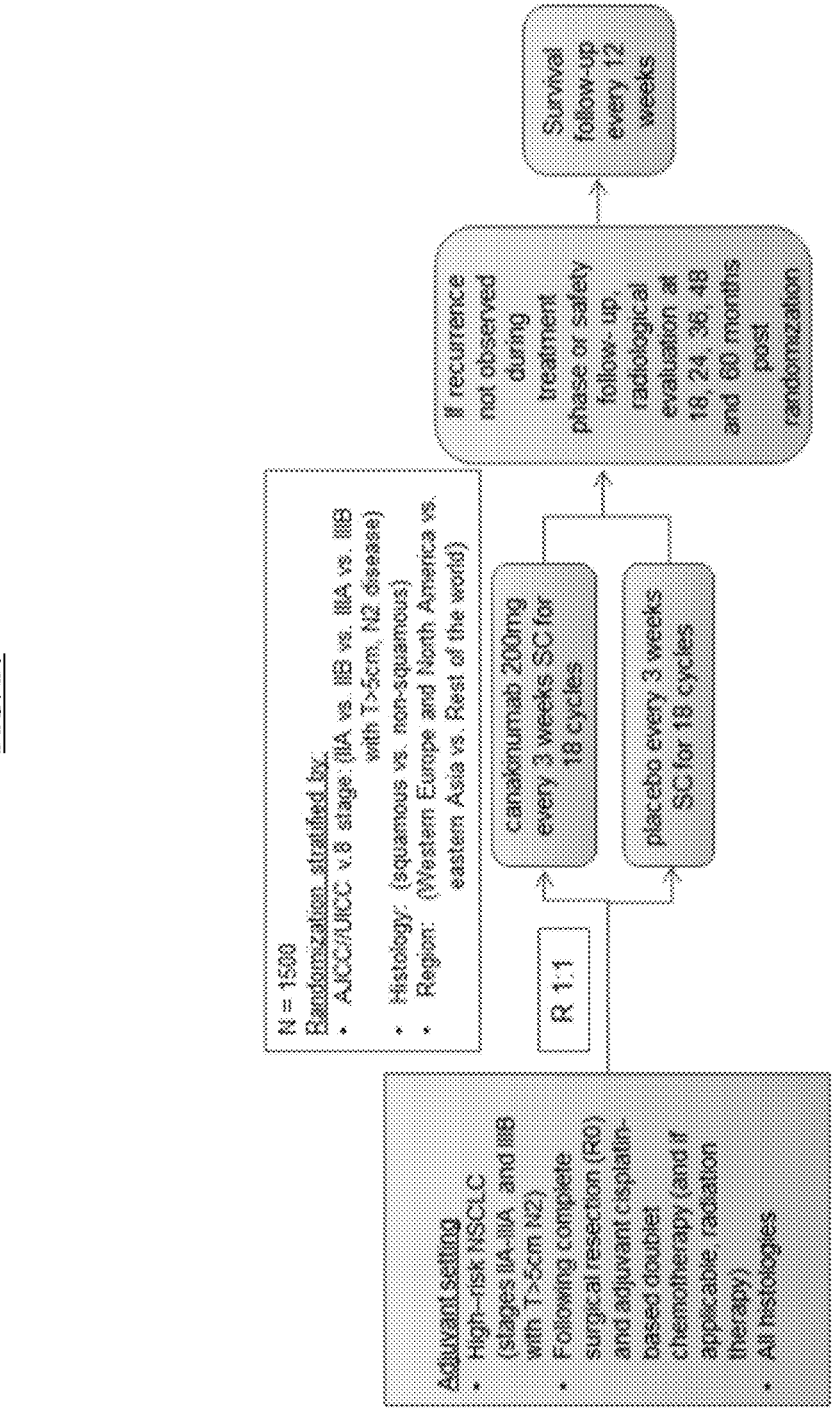

a
CD4+ and CD8+ T Cells
T cells per mg of Tumor
(Mean ± SEM)
Isotype CD4+
anti IL-1b CD4+
Isotype CD8+
anti IL-1b CD8+
b
FoxP3+ T Cells
Frequency of FoxP3+ Positive Cells
(Mean ± SEM)
c
Myeloid Cells
% of Single Cells
(Mean ± SEM)
Isotype - Neutrophils
anti IL-1b - Neutrophils
Isotype - TAM2
anti IL-1b - TAM2
d
CD4 Subsets
LL2
Frequency of Populations
(% of CD4+)
Isotype
anti-1b
FoxP3+
Helios+
FoxP3+Helios+
e
Myeloid Cells
LL2
Calsing of tumor
(Mean ± SEM)
TAM2
Neutrophils

FIG. 20


Adjuvant setting
High-risk NSCLC (stages IIA-IIA and IIB with T>5cm N2)
Following complete surgical resection (R0) and adjuvant (cisplatin-based doublet chemotherapy) (and if applicable, radiation therapy)
All histotypes
N = 1500
Randomization stratified by:
AJCC/UICC v.8 stage (IIA vs. IIB vs. IIIA vs. IIIB with T>5cm, N2 disease)
Histology: (squamous vs. non-squamous)
Region: (Western Europe and North America vs. eastern Asia vs. Rest of the world)
R 1:1
canakinumab 200mg every 3 weeks SC for 18 cycles
placebo every 3 weeks SC for 18 cycles
If recurrence not observed during treatment phase or safety follow-up, radiological evaluation at 18, 24, 36, 48 and 60 months post randomization
Survival follow-up every 12 weeks

USE OF IL-1BETA BINDING ANTIBODIES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/649,631, filed on Mar. 29, 2018; U.S. Provisional Application No. 62/596,054, filed on Dec. 7, 2017; U.S. Provisional Application No. 62/550,307, filed on Aug. 25, 2017; U.S. Provisional Application No. 62/550,325, filed on Aug. 25, 2017; U.S. Provisional Application No. 62/529,515, filed on Jul. 7, 2017; and U.S. Provisional Application No. 62/523,458, filed on Jun. 22, 2017, each of which is hereby incorporated by reference in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing, which was submitted electronically in ASCII format via EFS-Web on Oct. 30, 2018, and is hereby incorporated by reference in its entirety.

TECHNICAL FIELD

[0003] The present invention relates to the use of an IL-1β binding antibody or a functional fragment thereof for the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer.

BACKGROUND OF THE DISCLOSURE

[0004] Lung cancer is one of the most common cancers worldwide among both men and women. Lung cancer is classified into two types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). The types are distinguished on the basis of histological and cytological observations, with NSCLC accounting for approximately 85% of lung cancer cases. Non-small cell lung cancer is further classified into subtypes, including but not limited to, squamous cell carcinoma, adenocarcinoma, bronchioalveolar carcinoma, and large cell (undifferentiated) carcinoma. Despite a variety of treatment option, the 5-year survival rates are only between 10% and 17%. Thus, there remains a continued need to develop new treatment options for lung cancer.

[0005] Similarly, although the current standard of care has provided significant outcome improvement for other cancers having at least a partial inflammatory basis, the vast majority of patients have incurable disease with limited survival for patients who progressed on chemotherapy.

SUMMARY OF THE DISCLOSURE

[0006] The present disclosure relates to the use of an IL-1β binding antibody or a functional fragment thereof, for the treatment and/or prevention of cancers that have at least a partial inflammatory basis, especially lung cancer. Typically other cancers that have at least a partial inflammatory basis include colorectal cancer (CRC), melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma, acute myeloblastic leukemia (AML), and biliary tract cancer.

[0007] An object of the present invention is to provide a therapy to improve the treatment of cancer having at least a partial inflammatory basis, including lung cancer. The present invention therefore relates to a novel use of an IL-1β binding antibody or a functional fragments thereof, suitably canakinumab, suitably gevokizumab, for the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer. In another aspect, the present invention relates to a particular clinical dosage regimen for the administration of an IL-1β binding antibody or a functional fragment thereof for the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer. In another aspect the subject with cancer having at least a partial inflammatory basis, including lung cancer, is administered with one or more chemotherapeutic agent and/or have received/will receive debulking procedures in addition to the administration of an IL-1β binding antibody or a functional fragment thereof.

[0008] There are also provided methods of treating or preventing cancer having at least a partial inflammatory basis, including lung cancer, in a human subject in need thereof comprising administering to the subject a therapeutically effective amount of an IL-1β binding antibody or a functional fragment thereof.

[0009] Another aspect of the invention is the use of an IL-1β binding antibody or a functional fragment thereof for the preparation of a medicament for the treatment of cancer having at least a partial inflammatory basis, including lung cancer.

[0010] The present disclosure also provides a pharmaceutical composition comprising a therapeutically effective amount of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab, for use in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, in a patient.

[0011] The present invention also relates to high sensitivity C-reactive protein (hsCRP) for use as a biomarker in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, in a patient. In a further aspect the invention relates to high sensitivity C-reactive protein (hsCRP) for use as a biomarker in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, in a patient, wherein said patient is treated with an IL-1β inhibitor, an IL-1β binding antibody or a functional fragment thereof.

[0012] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a male patient in need thereof in the treatment and/or prevention of a cancer having at least partial inflammatory basis, including lung cancer.

[0013] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment and/or prevention of a cancer having at least partial inflammatory basis, excluding lung cancer. Each and every embodiments disclosed in this application applies, separately or in combination, to this aspect.

[0014] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment and/or prevention of a cancer having at least partial inflammatory basis, excluding breast cancer. Each and every embodiments disclosed in this application applies, separately or in combination, to this aspect.

[0015] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment and/or prevention of a cancer having at least partial inflammatory basis, excluding lung cancer and corrolectal cancer. Each and every embodiments disclosed in this application applies, separately or in combination, to this aspect.

FIGURE LEGENDS

[0016] FIG. **1**. CANTOS trial profile.

[0017] FIGS. **2-4**. Cumulative incidence of fatal cancer (FIG. **2**), lung cancer (FIG. **3**), and fatal lung cancer (FIG. **4**) among CANTOS participants randomly allocated to placebo, canakinumab 50 mg, canakinumab 150 mg, or canakinumab 300 mg.

[0018] FIG. **5**. Forest plot for hazard ratio (confirmed lung cancer patients)—300 mg vs placebo.

[0019] FIG. **6**. Median change from baseline in hsCRP at month 3 by treatment arm (confirmed Lung cancer analysis set).

[0020] FIG. **7**. In vivo model of spontaneous human breast cancer metastasis to human bone predicts a key role for IL-1β signaling in breast cancer bone metastasis. Two 0.5 cm^3 pieces of human femoral bone were implanted subcutaneously into 8-week old female NOD SCID mice (n=10/group). 4 weeks later luciferase labelled MDA-MB-231-luc2-TdTomato or T47D cells were injected into the hind mammary fat pads. Each experiment was carried out 3-separate times using bone form a different patient for each repeat. Histograms showing fold change of IL-1B, IL-1R1, Caspase 1 and IL-1Ra copy number (dCT) compared with GAPDH in tumour cells grown in vivo compared with those grown in a tissue culture flask (a i); mammary tumours that metastasise compared with mammary tumours that do not metastasise (a ii); circulating tumour cells compared with tumour cells that remain in the fat pad (a iii) and bone metastases compared with the matched primary tumour (a iv). Fold change in IL-1β protein expression is shown in (b) and fold change in copy number of genes associated with EMT (E-cadherin, N-cadherin and JUP) compared with GAPDH are shown in (c). *=P<0.01**=P<0.001, ***=P<0.0001, ^^^=P<0.001 compared with naïve bone.

[0021] FIG. **8**. Stable transfection of breast cancer cells with IL-1B. MDA-MB-231, MCF7 and T47D breast cancer cells were stably transfected with IL-1B using a human cDNA ORF plasmid with a C-terminal GFP tag or control plasmid. a) shows pg/ng IL-1β protein from IL-1β-positive tumour cell lysates compared with scramble sequence control. b) shows pg/ml of secreted IL-1β from 10.000 IL-1β+ and control cells as measured by ELISA. Effects of IL-1B overexpression on proliferation of MDA-MB-231 and MCF7 cells are shown in (c and d) respectively. Data shown are mean+/−SEM, *=P<0.01, **=P<0.001, ***=P<0.0001 compared with scramble sequence control.

[0022] FIG. **9**. Tumour derived IL-1β induces epithelial to mesenchymal transition in vitro. MDA-MB-231, MCF7 and T47D cells were stably transfected with to express high levels of IL-1B, or scramble sequence (control) to assess effects of endogenous IL-1B on parameters associated with metastasis. Increased endogenous IL-1B resulted tumour cells changing from an epithelial to mesenchymal phenotype (a). b) shows fold-change in copy number and protein expression of IL-1B, IL-1R1, E-cadherin, N-cadherin and JUP compared with GAPDH and β-catenin respectively. Ability of tumour cells to invade towards osteoblasts through Matrigel and/or 8 μM pores, are shown in (c) and capacity of cells to migrate over 24 and 48h is shown using a wound closure assay (d). Data are shown as mean+/−SEM, *=P<0.01, **=P<0.001, ***=P<0.0001.

[0023] FIG. **10**. Pharmacological blockade of IL-1B inhibits spontaneous metastasis to human bone in vivo. Female NOD-SCID mice bearing two 0.5 cm^3 pieces of human femoral bone received intra-mammary injections of MDA-MB-231Luc2-TdTomato cells. One week after tumour cell injection mice were treated with 1 mg/kg/day IL-1Ra, 20 mg/kg/14-days canakinumab, or placebo (control) (n=10/group). All animals were culled 35 days following tumour cell injection. Effects on bone metastases (a) were assessed in vivo and immediately post-mortem by luciferase imaging and confirmed ex vivo on histological sections. Data are shown as numbers of photons per second emitted 2 minutes following sub-cutaneous injection of D-luciferin. Effects on numbers of tumour cells detected in the circulation are shown in (b). *=P<0.01, **=P<0.001, ***=P<0.0001.

[0024] FIG. **11**. Tumour derived IL-1B promotes breast cancer bone homing in vivo. 8-week old female BALB/c nude mice were injected with control (scramble sequence) or IL-1B overexpressing MDA-MB-231-IL-1B+ cells via the lateral tail vein. Tumour growth in bone and lung were measured in vivo by GFP imaging and findings confirmed ex vivo on histological sections. a) shows tumour growth in bone; b) shows representative μCT images of tumour bearing tibiae and the graph shows bone volume (BV)/tissue volume (TV) ratio indicating effects on tumour induced bone destruction; c) shows numbers and size of tumours detected in lungs from each of the cell lines. *=P<0.01, **=P<0.001, ***=P<0.0001. (B=bone, T=tumour, L=lung)

[0025] FIG. **12**. Tumour cell-bone cell interactions stimulate IL-1B production cell proliferation. MDA-MB-231 or T47D human breast cancer cell lines were cultured alone or in combination with live human bone, HS5 bone marrow cells or OB1 primary osteoblasts. a) shows the effects of culturing MDA-MB-231 or T47D cells in live human bone discs on IL-1β concentrations secreted into the media. The effect of co-culturing MDA-MB-231 or T47D cells with HS5 bone cells on IL-1β derived from the individual cell types following cell sorting and the proliferation of these cells are shown in b) and c). Effects of co-culturing MDA-MB-231 or T47D cells with OB1 (osteoblast) cells on proliferation are shown in d). Data are shown as mean+/−SEM. *=P<0.01, **=P<0.001, ***=P<0.0001.

[0026] FIG. **13**. IL-1β in the bone microenvironment stimulates expansion of the bone metastatic niche. Effects of adding 40 pg/ml or 5 ng/ml recombinant IL-1β to MDA-MB-231 or T47D breast cancer cells is shown in (a) and effects on adding 20 pg/ml, 40 pg/ml or 5 ng/ml IL-1B on proliferation of HS5, bone marrow, or OB1, osteoblasts, are shown in b) and c) respectively. (d) IL-1 driven alterations to the bone vasculature was measured following CD34 staining in the trabecular region of the tibiae from 10-12-week old female IL-1R1 knockout mice. (e) BALB/c nude mice treated with 1 mg/ml/day IL-1Ra for 31 days and (f) C57BL/6 mice treated with 10 μM canakinumab for 4-96h. Data are shown as mean+/−SEM, *=P<0.01, **=P<0.001, ***=P<0.0001.

[0027] FIG. **14**. Suppression of IL-1 signalling affects bone integrity and vasculature. Tibiae and serum from mice that do not express IL-1R1 (IL-1R1 KO), BALB/c nude

mice treated daily with 1 mg/kg per day of IL-1R antagonist for 21 and 31 days and C57BL/6 mice treated with 10 mg/kg of canakinumab (Ilaris) of 0-96h were analysed for bone integrity by μCT and vasculature using ELISA for Endothelin 1 and pan VEGF. a) shows the effects of IL-1R1 KO; b) effects of Anakinra and c) effects of canakinumab on bone volume compared with tissue volume (i), concentration of Endothelin 1 (ii) and concentrations of VEGF secreted into the serum. Data shown are mean+/−SEM, *=P<0.01, **=P<0.001, ***=P<0.0001 compared with control.

[0028] FIG. **15**. Tumour derived IL-1β predicts future recurrence and bone relapse in patients with stage II and III breast cancer. ~1300 primary breast cancer samples from patients with stage II and III breast cancer with no evidence of metastasis were stained for 17 kD active IL-1β. Tumours were scored for IL-1β in the tumour cell population. Data shown are Kaplan Meyer curves representing the correlation between tumour derived IL-1β and subsequent recurrence a) at any site or b) in bone over a 10-year time period.

[0029] FIG. **16**. Simulation of canakinumab PK profile and hsCRP profile. a) shows canakinumab concentration time profiles. Solid line and band: median of individual simulated concentrations with 2.5-97.5% prediction interval (300 mg Q12W (bottom line), 200 mg Q3W (middle line), and 300 mg Q4W (top line)). b) shows the proportion of month 3 hsCRP being below the cut point of 1.8 mg/L for three different populations: all CANTOS patients (scenario 1), confirmed lung cancer patients (scenario 2), and advanced lung cancer patients (scenario 3) and three different dose regimens. c) is similar to b) with the cut point being 2 mg/L. d) shows the median hsCRP concentration over time for three different doses. e) shows the percent reduction from baseline hsCRP after a single dose.

[0030] FIG. **17**. Gene expression analysis by RNA sequencing in colorectal cancer patients receiving PDR001 in combination with canakinumab, PDR001 in combination with everolimus and PDR001 in combination with others. In the heatmap figure, each row represents the RNA levels for the labelled gene. Patient samples are delineated by the vertical lines, with the screening (pre-treatment) sample in the left column, and the cycle 3 (on-treatment) sample in the right column. The RNA levels are row-standardized for each gene, with black denoting samples with higher RNA levels and white denoting samples with lower RNA levels. Neutrophil-specific genes FCGR3B, CXCR2, FFAR2, OSM, and G0S2 are boxed.

[0031] FIG. **18**. Clinical data after gevokizumab treatment (panel a) and its extrapolation to higher doses (panels b, c, and d). Adjusted percent change from baseline in hsCRP in patients in a). The hsCRP exposure-response relationship is shown in b) for six different hsCRP base line concentrations. The simulation of two different doses of gevokizumab is shown in b) and c).

[0032] FIG. **19**. Effect of anti-IL-beta treatment in two mouse models of cancer. a), b), and c) show data from the MC38 mouse model, and d) and e) show data from the LL2 mouse model.

[0033] FIG. **20**. Graphic showing design of phase III study CACZ885T2301.

DETAILED DESCRIPTION OF THE DISCLOSURE

[0034] Many malignancies arise in areas of chronic inflammation (1) and inadequate resolution of inflammation is hypothesized to play a major role in tumor invasion, progression, and metastases (2-4). Inflammation is of particular pathophysiologic relevance for lung cancer where chronic bronchitis, triggered by asbestos, silica, smoking, and other external inhaled toxins, results in a persistent pro-inflammatory response (5,6). Inflammatory activation in the lung is mediated in part through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome with consequent local production of interleukin-1β (IL-1β), a process that can lead to both chronic fibrosis and cancer (7, 8). In murine models, inflammasome activation and IL-1β production can accelerate tumor invasiveness, growth, and metastatic spread (2). For example, in IL-1β−/− mice, neither local tumors nor lung metastases develop following localized or intravenous inoculation with melanoma cell lines, data suggesting that IL-1β may be essential for the invasiveness of already existing malignancies (9). It has thus been hypothesized that inhibition of IL-1β might have an adjunctive role in the treatment of cancers that have at least a partial inflammatory basis (10-13).

[0035] The present invention arose from the analysis of the data generated from the CANTOS trial, which is a randomized, double-blind, placebo-controlled, event-driven trial. CANTOS was designed to evaluate whether the administration of quarterly subcutaneous canakinumab can prevent recurrent cardiovascular events among stable post-myocardial infarction patients with elevated hsCRP. The enrolled 10,061 patients with myocardial infarction and inflammatory atherosclerosis were free of previously diagnosed cancer and had high sensitivity C-reactive protein (hsCRP)≥2 mg/L. Three escalating canakinumab doses (50 mg, 150 mg, and 300 mg given subcutaneously every 3 months) were compared to placebo. Participants were followed for incident cancer diagnoses over a median follow-up period of 3.7 years.

[0036] Patient Population Patients were eligible for enrollment in CANTOS if they had a prior history of myocardial infarction and had blood levels of hsCRP≥2 mg/L despite use of aggressive secondary prevention strategies. As canakinumab is a systemic immunomodulatory agent, the trial was designed to exclude from enrollment those with a history of chronic or recurrent infections, prior malignancy other than basal cell skin carcinoma, suspected or known immunocompromised states, a history of or at high risk for tuberculosis or HIV-related disease, or ongoing use of systemic anti-inflammatory treatments.

[0037] Randomization (FIG. **1**) Based on experience from a phase lib study (19), an "anchor dose" was initially selected for canakinumab of 150 mg SC every three months. In addition, a higher dose of 300 mg given twice over a two-week period and then every three months was also initially selected to address theoretical concerns regarding IL-1β auto-induction. As such, when the first patient was screened on Apr. 11, 2011, CANTOS was initiated as a three-arm trial comparing standard of care plus placebo to either standard of care plus canakinumab 150 mg or canakinumab 300 mg with participants allocated to each study arm in a 1:1:1 ratio. However, following health authority feedback requiring broader dose-response data, a lower dose canakinumab arm was introduced into the trial (50 mg SC every three months). The protocol was thus amended and a formal four arm structure was approved in July of 2011 but varied in the timing of its adoption by region and site.

[0038] To accommodate this structural change, the proportion of individuals who ultimately would be allocated to placebo was increased as was the proportion moving forward who would be randomly allocated to the 50 mg dose. Thus, the treatment allocation ratios were altered from 1:1:1 for placebo:150 mg canakinumab:300 mg canakinumab for the first 741 participants recruited to 2:1.4:1.3:1.3 for placebo:50 mg canakinumab:150 mg canakinumab:300 mg canakinumab, respectively, for the remaining 9,320 participants. Trial enrolment was completed in March 2014 and all participants followed until May 2017.

[0039] Per protocol, all CANTOS participants had complete blood counts, lipid panels, hsCRP, and measures of renal and hepatic function performed at baseline and at 3, 6, 9, 12, 24, 36, and 48 months after randomization.

[0040] Endpoint Clinical endpoints of interest for the analysis were any incident cancers diagnosed and reported during trial follow-up. For any such event, medical records were obtained and the cancer diagnosis reviewed by a panel of oncologists unaware of study drug allocation. Where possible, a primary source was noted, as were any evidence of site-specific metastases. Cancers were also classified as fatal or non-fatal by the trial endpoint committee.

[0041] Statistical Analysis Cox proportional hazard models were used to analyze the incidence of cancer overall in the canakinumab and placebo groups, as well as the incidence of fatal and non-fatal cancer, and cancer incidence on a site specific basis. For proof-of-concept purposes and consistent with analyses conducted throughout the trial for all Data and Safety Monitoring Board meetings, comparisons were made between incidence rates on placebo to incidence rates for each individual canakinumab dose, across ascending canakinumab doses (with scores 0, 1, 3, and 6 proportional to dose), and for the combined active canakinumab treatment groups.

Results

[0042] CANTOS was shown to meet the primary endpoint, demonstrating that when used in combination with standard of care, ACZ885 reduces the risk of major adverse cardiovascular events (MACE) in patients with a prior heart attack and inflammatory atherosclerosis. MACE is a composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke. ACZ885 has been shown to reduce cardiovascular risk in people with a prior heart attack by selectively targeting inflammation.

[0043] Patients Baseline clinical characteristics of the 10,061 CANTOS participants are provided in Table 1 for those who did or did not develop a diagnosis of cancer during trial follow-up.

[0044] Compared to those who were not diagnosed with cancer, those who developed incident lung cancers were older (P<0.001), more likely to be current smokers (P<0.001). Consistent with prior work indicating a strong inflammatory component to certain cancers, median hsCRP levels were elevated at baseline among those who were diagnosed with lung cancer during follow-up compared to those who remained free of any cancer diagnosis (6.0 versus 4.2 mg/L, P<0.001). Similar data were observed for interleukin-6 (3.2 versus 2.6 ng/L, P<0.0001).

[0045] During trial follow-up, as compared to placebo, canakinumab was associated with dose-dependent reductions in hsCRP of 27 to 40 percent (all P-values<0.0001) and with dose-dependent reductions in IL-6 of 25 to 43 percent (all P-values<0.0001). Canakinumab had no effect on LDL or HDL cholesterol.

[0046] Effects on Total Cancer Events and on Fatal Cancer Events Incidence rates for any cancer in the placebo, 50 mg, 150 mg, and 300 mg canakinumab groups were 1.84, 1.82, 1.68, and 1.72 per 100 person-years, respectively (P across canakinumab dose groups compared to placebo=0.34). By contrast, a statistically significant dose-dependent effect was observed for fatal cancers where incidence rates in the placebo, 50 mg, 150 mg, and 300 mg groups were 0.64, 0.55, 0.50, and 0.31 per 100 person-years, respectively (P across canakinumab dose groups compared to placebo=0.001) (Table 2).

[0047] Effects on Lung Cancer Over the median 3.7 year follow-up period, random allocation to canakinumab was associated with statistically significant dose-dependent reductions in total cancer mortality. For this endpoint (N=196), referent to placebo, hazard ratios (95% confidence interval, P-value) were 0.86 (0.59-1.24, P=0.42), 0.78 (0.54-1.13, P=0.19), and 0.49 (0.31-0.75, P=0.0009) for the canakinumab 50 mg, 150 mg, and 300 mg groups, respectively. These data correspond to incidence rates in the placebo, 50 mg, 150 mg, and 300 mg groups of 0.64, 0.55, 0.50, and 0.31 per 100 person-years, respectively (P-trend across active dose groups compared to placebo=0.0007) (Table 2 and FIG. **2**).

This effect was largely due to reductions in lung cancer; among those assigned to placebo, 26.0% of all cancers and 47% of all cancer deaths were lung cancers, whereas among those assigned to canakinumab, 16% of all cancers and 34% of cancer deaths were lung cancers. For incident lung cancer (N=129), referent to placebo, hazard ratios (95% confidence interval, P-value) were 0.74 (0.47-1.17, P=0.20), 0.61 (0.39-0.97, P=0.034, and 0.33 (0.18-0.59, P=0.0001) for the canakinumab 50 mg, 150 mg, and 300 mg groups, respectively. These data correspond to incidence rates in the placebo, 50 mg, 150 mg, and 300 mg groups of 0.49, 0.35, 0.30, and 0.16 per 100 person-years, respectively (P-trend across active dose groups compared to placebo<0.0001) (Table 2 and FIG. **3**).

[0048] Stratification by smoking indicated slightly greater relative benefits of canakinumab on lung cancer among current as compared to past smokers (HR 0.50. P=0.005 for current smokers; HR 0.61. P=0.006 for past smokers). This effect was more prominent for the highest canakinumab dose (HR 0.25, P=0.002 for current smokers; HR 0.44, P=0.025 for past smokers, Table S2).

[0049] For lung cancer mortality (N=77), referent to placebo, hazard ratios (95% confidence interval, P=value) were 0.67 (0.37-1.20, P=0.18), 0.64 (0.36-1.14, P=0.13), and 0.23 (0.10-0.54, P=0.0002) for the canakinumab 50 mg, 150 mg, and 300 mg groups, respectively. These data correspond to incidence rates in the placebo, 50 mg, 150 mg, and 300 mg groups of 0.30, 0.20, 0.19, and 0.07 per 100 person-years, respectively (P-trend across active dose groups compared to placebo=0.0002) (Table 2 and FIG. **4**).

[0050] Benefits of canakinumab were evident in patients for whom lung cancer type was unspecified or where histology indicated adenocarcinoma or poorly differentiated large cell cancers (incidence rates in the placebo, canakinumab 50 mg, 150 mg, and 300 mg dose groups were 0.41, 0.33, 0.27, and 0.12, respectively [P-trend across dose groups compared to placebo=0.0004]). Power was limited to

definitively address effects of canakinumab in cases where histology indicated small cell lung cancers or squamous cell carcinomas (Table S3). In analyses of combined canakinumab doses, risk reductions for total lung cancer were greater for those who had reductions in hsCRP greater than or equal to the median value at 3 months. Specifically, compared to placebo, the observed hazard ratio for lung cancer among those who achieved hsCRP reductions greater than the median value of 1.8 mg/L at 3 months was 0.29 (95% CI 0.17-0.51, P<0.0001), better than the effect observed for those who achieved hsCRP reductions less than the median value (HR 0.83, 95% CI 0.56-1.22, P=0.34). Similar effects were observed for median IL-6 levels achieved at 3 months.

[0051] While the CANTOS protocol was designed to exclude individuals with prior non-basal cell malignancies, 76 of 10,061 (0.8%) were found on detailed record review to have had prior cancers. Post-hoc exclusion of these individuals had no impact on the above results.

[0052] Adverse Events With regard to bone marrow function, thrombocytopenia and neutropenia were rare but more common among those allocated to canakinumab (Table 3). As reported elsewhere (20), while there was no increase in rates of total infections, there were increased rates of cellulitis and *Clostridium difficile* colitis and an increase in fatal events attributed to infection or sepsis when the three canakinumab groups were pooled and compared to placebo (incidence rates 0.31 versus 0.18 per 100 person years, P=0.023). Participants succumbing to infection tended to be older and more likely to have diabetes. Despite this adverse effect, both non-cardiovascular mortality (HR 0.97, 95% CI 0.79-1.19, P=0.80) and all-cause mortality (HR 0.94, 95% CI 0.83-1.06, P=0.31) were non-significantly reduced. Serious tuberculosis infections were rare and occurred at similar rates in the canakinumab and placebo treated groups (0.06%). Injection site reactions occurred with similar frequency in the canakinumab and placebo groups. Consistent with known effects of IL-1β inhibition, canakinumab resulted in significant reductions in adverse reports of arthritis, gout, and osteoarthritis (Table 4).

[0053] In these randomized, double-blind, placebo controlled trial data, inhibition of IL-1β with canakinumab over a median period of 3.7 years markedly reduced the rate of fatal and non-fatal lung cancer among atherosclerosis patients with elevated hsCRP who did not have a prior diagnosis of cancer. Effects were dose dependent with relative hazard reductions of 67% (P=0.0001) and 77% (P=0.0002) for total lung cancer and fatal lung cancer, respectively, among those randomly allocated to the highest canakinumab dose (300 mg SC every 3 months). Beneficial effects of canakinumab were observed on incident lung cancers within weeks of initiating therapy, again particularly at the highest canakinumab dose. Patients with elevated levels of the inflammatory biomarkers hsCRP and interleukin-6 were at highest risk for incident lung cancer and appeared to gain the most benefit, as did current smokers. By contrast, canakinumab had non-significant effects on site-specific cancers other than lung cancer. Yet for those randomly allocated to canakinumab 300 mg SC, total cancer mortality fell by half (P=0.0009).

[0054] CANTOS was an inflammation reduction trial conducted among post-myocardial infarction patients with elevated hsCRP and high rates of current or past smoking (17). These characteristics put the CANTOS population at higher than average risk for lung cancer and afforded the additional opportunity reported here to address the effect of interleukin-1β inhibition on cancer. However, by design, there are no data for individuals free of atherosclerotic disease or with low levels of hsCRP.

[0055] While possible, it is perhaps unlikely that canakinumab had any direct effects on oncogenesis and the development of new lung cancers. Patients who developed lung cancer during follow-up were 65 years of age on average on study entry and more than 906 were current or past smokers. Further, the average follow-up time is unlikely to be adequate to demonstrate a reduction in new cancers.

Rather, it seems far more likely that canakinumab—a powerful inhibitor of interleukin-1β—substantially reduced the rate of progression, invasiveness, and metastatic spread of lung cancers that were prevalent but undiagnosed at trial entry. In this regard, the clinical data are consistent with prior experimental work indicating that cytokines such as IL-1β can promote angiogenesis and tumor growth and that IL-1β is required for tumor invasiveness of already existing malignant cells (2-4,9). In murine models, high IL-1β concentrations within the tumor micro-environment are associated with more virulent phenotypes (13) and secreted IL-1β derived from this microenvironment (or directly from malignant cells) can promote tumor invasiveness and in some cased induce tumor-mediated suppression (2,9,21).

Breast cancer bone metastases is incurable and associates with poor prognosis in patients. Bone metastases occur when tumor cells are disseminated into the bone marrow and take up residence in the bone metastatic niche. This niche is thought to be made up of three interacting niches: the osteoblastic, vascular and hematopoietic stem cell niche (reviewed by (Massague and Obenauf, 2016; Weilbaecher et al., 2011)). Evidence from metastases in other organs predicts that proliferation of vascular endothelial cells and sprouting of new blood vessels may also promote proliferation of tumor cells in bone driving metastases formation (Carbonell et al., 2009; Kienast et al., 2010). It was previously shown that bone seeking breast cancer cell lines, MDA-IV produce high concentrations of IL-1β compared to parental MDA-MB-231 cells (Nutter et al., 2014). Similarly, in a PC3 model of prostate cancer genetic overexpression of IL-1 increased bone metastases from tumor cells injected into the heart whereas genetic knockdown of this molecule reduced bone metastasis (Liu et al., 2013).

[0056] Since the time of Virchow, inflammation has been linked to cancer; as Balkwill and Mantovani have written, 'if genetic damage is "the match that lights the fire" of cancer, some types of inflammation may provide the "fuel that feeds the flames"' (22). This hypothesis helps to explain, in part, why the chronic use of aspirin as well as other non-steroidal anti-inflammatory agents is associated with reduced fatality rates from colorectal cancer and lung adenocarcinomas (23,24). However, in contrast to these agents which require a decade or more of use to show efficacy, beneficial effects of canakinumab on lung cancer incidence and lung cancer mortality were observed in a trial with much shorter time frame. The apparent beneficial effects of canakinumab were observed within weeks of initiating therapy. The specificity of canakinumab in the data for lung cancer and its augmented effect among current smokers is of particular interest given the fact that inflammasome mediated production of

IL-1β is triggered by multiple inhaled environmental toxins known to induce local pulmonary inflammation as well as cancer (7,8).

[0057] The trial was not designed as a cancer treatment study. Rather, by design, the trial enrolled atherosclerosis patients without a prior history of cancer. There is precedent for such an IL-1 targeted cytokine approach for other cancer types. For example, the IL-1 receptor antagonist anakinra has been reported in a case series of 47 patients to modestly reduce the progression of smoldering or indolent myeloma (25). In a second case series of 52 patients with diverse metastatic cancers, a human monoclonal antibody targeting IL-1α was well tolerated and showed modest improvement in lean body mass, appetite, and pain (26).

In conclusion, these randomized placebo-controlled trial data provide evidence that inhibiting innate immune function with canakinumab, a monoclonal antibody that targets IL-1β, substantially reduces incident lung cancer and lung cancer fatality.

[0058] Thus in one aspect, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof (DRUG of the invention), suitably canakinumab or a functional fragment thereof (included in DRUG of the invention), gevokizumab or a functional fragment thereof (included in DRUG of the invention), for the treatment and/or prevention of cancers that have at least a partial inflammatory basis, especially lung cancer.

[0059] In one embodiment the lung cancer has concomitant inflammation activated or mediated in part through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome with consequent local production of interleukin-1β.

[0060] Advanced studies in delineating interaction between tumor and the tumor microenvironment have revealed that chronic inflammation can promote tumor development, and tumor fuels inflammation to facilitate tumor progression and metastasis. Inflammatory microenvironment with cellular and non-cellular secreted factors provides a sanctuary for tumor progression by inducing angiogenesis; recruiting tumor promoting, immune suppressive cells and inhibiting immune effector cell mediated antitumor immune response. One of the major inflammatory pathways supporting tumor development and progression is IL-1β, a pro-inflammatory cytokine produced by tumor and tumor associated immune suppressive cells including neutrophils and macrophages in tumor microenvironment.

[0061] The meaning of "cancers that have at least a partial inflammatory basis" or "cancer having at least a partial inflammatory basis" is well known in the art. In one embodiment, the term as used herein refers to any cancer in which the IL-1β mediated inflammatory responses contribute to the tumor development and/or propagation, including but not necessarily limited to metastasis. It is quite common that such cancer has concomitant inflammation activated or mediated in part through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome with consequent local production of interleukin-1β. It is quite common that in a patient with such cancer, the expression, or even the overexpression of IL-1β can be detected, commonly at the site of the tumor, especially in the surrounding tissue of the tumor, in comparison to normal tissue. The expression of IL-1β can be detected by routine methods, such as immunostaining, ELISA based assays, ISH, RNA sequencing or RT-PCR in the tumor as well as in serum/plasma. The expression or higher expression of IL-1β can be concluded against negative control, usually normal tissue at the same site or higher than normal level of IL-1β. Simultaneously or alternatively, it is quite common that a patient with such cancer has chronic inflammation, which is manifested, typically, by higher than normal level of CRP or hsCRP, IL-6 and TNFα. Cancers that have at least a partial inflammatory basis include but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including gastric and intestinal cancer, cancer of the esophagus, particularly the lower part of the esophagus, renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer (including HPV, EBV and tobacco/alcohol induded head and neck cancer), bladder cancer, hepatocellular carcinoma (HCC), pancreatic cancer, ovarian cancer, cervical cancer, endometrial cancer, neuroendocrine cancer and biliary tract cancer (including bile duct and gallbladder cancers) as well as hematologic cancers such as acute myeloblastic leukemia (AML), myelofibrosis and multiple myeloma (MM).

[0062] Available techniques allow detection and quantification of IL-1β in tissue as well as in serum/plasma, especially when the IL-1β is expressed to a higher than normal level. For example, Using the R&D Systems high sensitivity IL-1b ELISA kit. IL-1β cannot be detected in majority of healthy donor serum samples.

Sample Values

[0063] Serum/Plasma—Samples from apparently healthy volunteers were evaluated for the presence of human IL-1β in this assay. No medical histories were available for the donors used in this study.

Sample Type	Mean of Detectable (pg/ml)	% Detectable	Range (pg/ml)
Serum (n = 50)	0.357	10	ND-0.606
EDTA plasma (n = 50)	0.292	12	ND-0.580
Heparin plasma (n = 50)	0.448	14	ND-1.08

ND = Non-detectable

[0064] Thus in a healthy person the IL-1β level is bearly detectable or just above the detection limit with the high sensitivity R&D IL-1β ELISA kit. It is expected that in patients with cancer having at least partial inflammatory basis the IL-1β level will be higher than normal and can be detected by the same kit. Taking the IL-1β expression level in a healthy person as the normal level (reference level), the term "higher than normal level of IL-1β" is understood as an IL-1β level that is higher than the reference level. Normally at least 2 fold, at least 5 fold, at least 10 fold, at least 15 fold, at least 20 fold of the reference level is considered as higher than normal level. Blocking IL-1β pathway normally triggers the compensating mechanism leading to more production of IL-1β. Thus the term "higher than normal level of IL-1β" refers to the level of IL-1β either prior to or post to the administration of an IL-1β inhibitor, preferably IL-1β binding antibody or a fragment thereof. Preferably the term "higher than normal level of IL-1β" refers to the level of IL-1β prior to the administration of IL-1β inhibitor. It is also observed that treatment of cancer with agents other than IL-1β inhibitors could result in more production of IL-1β. Thus the term "higher than normal level of IL-1β" refers to the level of IL-1β either prior to or post to the administration of said agents.

[0065] When using staining, such as immunstaining, to detect IL-1β expression in a tissue preparation, the term "higher than normal level of IL-1β" refers to that the staining signal generated by specific IL-1β protein or IL-1β RNA detecting molecule is distinguishably stronger than staining signal of the surrounding tissue not expressing IL-1β.

[0066] Inflammation component is universally present, albeit to different degrees, in the cancer development. Further cancers include but not limited to haematological malignancies, brain tumors, bone cancer and nose and throat cancer. Haematological malignancies are the types of cancer affecting blood, bone marrow and lymph nodes. They are referred to as leukaemia, lymphoma and myeloma depending on the type of cell affected. Leukemia includes Acute Lymphoblastic Leukemia (adult or childhood), Acute Myeloid Leukemia, (Adult and childhood), Chronic Lymphocytic Leukemia, Chronic Myelogenous Leukemia and Hairy Cell Leukemia. Lymphoma includes AIDS-Related Lymphoma, Cutaneous T-Cell Lymphoma (Mycosis Fungoides and the Sézary Syndrome), Hodgkin Lymphoma (Adult or childhood), Mycosis Fungoides, Non-Hodgkin Lymphoma (Adult or childhood), Primary Central Nervous System Lymphoma, sézary Syndrome, T-Cell Lymphoma, Cutaneous (Mycosis Fungoides and the Sézary Syndrome) and Waldenström Macroglobulinemia (Non-Hodgkin Lymphoma). Other haematological malignancies include Chronic Myeloproliferative Neoplasms, Langerhans Cell Histiocytosis, Multiple Myeloma, Plasma Cell Neoplasm, Myelodysplastic Syndromes and Myelodysplastic/Myeloproliferative Neoplasms.

[0067] Primary brain tumors include Anaplastic astrocytomas and glioblastomas, Meningiomas and other mesenchymal tumors, ituitary tumors, Schwannomas, CNS lymphomas, Oligodendrogliomas, Ependymomas, Low-grade astrocytomas, Medulloblastomas. Primary spinal tumors include Schwannomas, meningiomas, and ependymomas, Sarcomas, Astrocytomas, Vascular tumors, Chordomas and Neuroblastoma.

[0068] Liver cancer include Hepatocellular carcinoma, Intrahepatic cholangiocarcinoma (bile duct cancer), Angiosarcoma and hemangiosarcoma and Hepatoblastoma.

[0069] Nose and throat cancer are known collectively as head and neck cancers usually begin in the squamous cells that line the moist, mucosal surfaces inside the head and neck (for example, inside the mouth, the nose, and the throat). These squamous cell cancers are often referred to as squamous cell carcinomas of the head and neck. Cancers of the head and neck are further categorized by the area of the head or neck in which they begin: Oral cavity, Pharynx, Larynx, Paranasal sinuses and nasal cavity, Salivary glands.

[0070] In one embodiment, the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment and/or prevention of lung cancer, wherein the incidence rate for lung cancer is reduced by at least 30%, at least 40% or at least 50%, in comparison to patients not receiving such treatment.

[0071] Lung cancer includes small cell lung cancer and non-small cell lung cancer (NSCLC)/Non-small-cell lung carcinoma (NSCLC). NSCLC is any type of epithelial lung cancer other than small cell lung carcinoma (SCLC) and can be subclassified as squamous (~30%) or non-squamous (~70%; includes adenocarcinoma and large cell histologies) histological types. The term "NSCLC" includes but is not limited to adenocarcinoma of the lung (herein referred to as "adenocarcinoma"), poorly differentiated large cell carcinoma, squamous cell (epidermoid) lung carcinoma, adenosquamous carcinoma and sarcomatoid carcinoma and bronchioalveolar carcinoma. Lung cancer also includes metastases to lung and small cell lung cancer. In one embodiment of the invention, the lung cancer is small cell lung cancer. In another embodiment, the lung cancer is NSCLC. In one embodiment the lung cancer is adenocarcinoma of the lung. In another embodiment the lung cancer is poorly differentiated large cell carcinoma in lung. In another embodiment the lung cancer is non-squamous lung cancer. In another embodiment of the invention the lung cancer is squamous cell (epidermoid) lung carcinoma. In yet another embodiment, the lung cancer is selected from the group consisting of adenosquamous carcinoma or sarcomatoid carcinoma or metastases to lung.

[0072] As used herein, the terms "treat", "treatment" and "treating" refer to the reduction or amelioration of the progression, severity and/or duration of a disorder, e.g., a proliferative disorder, or the amelioration of one or more symptoms, suitably of one or more discernible symptoms, of the disorder resulting from the administration of one or more therapies. In specific embodiments, the terms "treat", "treatment" and "treating" refer to the amelioration of at least one measurable physical parameter of a proliferative disorder, such as growth of a tumor, not necessarily discernible by the patient. In other embodiments the terms "treat", "treatment" and "treating" refer to the inhibition of the progression of a proliferative disorder, either physically by, e.g., stabilization of a discernible symptom, physiologically by, e.g., stabilization of a physical parameter, or both. In other embodiments the terms "treat", "treatment" and "treating" refer to the reduction or stabilization of tumor size or cancerous cell count. As far as cancers that have at least a partial inflammatory basis are concerned, taking lung cancer as an example, the term treatment refers to at least one of the following: alleviating one or more symptoms of lung cancer, delaying progression of lung cancer, shrinking tumor size in lung cancer patient, inhibiting lung cancer tumor growth, prolonging overall survival, prolonging progression free survival, preventing or delaying lung cancer tumor metastasis, reducing (such as eradiating) preexisting lung cancer tumor metastasis, reducing incidence or burden of preexisting lung cancer tumor metastasis, or preventing recurrence of lung cancer.

[0073] NSCLC is staged according to established guidelines, for example AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017, summarized by Goldstraw P. et al. The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. Journal of Thoracic Oncology 2016:11(1):39-51). Stage I is characterized by a localized tumor, which has not spread to any lymph nodes. Stage II is characterized by a localized tumor, which has spread to a lymph node contained within the surrounding part of the lung. In general, stage I or II are regarded as early stage as they display a size and location amenable for surgical removal.

[0074] Stage III is characterized by a localized tumor, which has spread to a regional lymph node not contained within the lung, for example, a mediastinal lymph node. Stage III is further divided into two substages: stage IIIA, in which the lymph node metastasis is on the same side of the

lung as the primary tumor, and stage IIIB, in which the cancer has spread to the opposite lung, to a lymph node above the collarbone, to the fluid surrounding the lungs, or in which the cancer grows into a vital structure of the chest. Stage IV is characterized by spreading of the cancer to different sections (lobes) of the lung, or to distant sites within the body, for example, to the brain, the bones, the liver, and/or in the adrenal glands.

[0075] In a preferred embodiment, the patient has early stage of lung cancer, especially NSCLC. In a preferred embodiment, the patient has been diagnosed with lung cancer after imaging based lung cancer screening. In another embodiment, the lung cancer is an advanced, metastatic, relapsed, and/or refractory lung cancer. In one embodiment, the patient has stage IA NSCLC. In one embodiment, the patient has stage IB NSCLC. In one embodiment, the patient has stage IIA NSCLC. In one embodiment, the patient has stage IIB NSCLC. In one embodiment, the patient has stage IIIA NSCLC. In one embodiment, the patient has stage IIIB NSCLC. In a further embodiment, the patient has stage IV NSCLC.

In one embodiment, the patient is a smoker, including current smoker and past smoker. The CANTOS trial data are consistent with the general conception that there is a higher lung cancer incidence among smokers than non-smokers. While both current smoker and past smoker have reduced hazard ratio in the treatment group compared to placebo, stratification by smoking indicated greater relative benefits of canakinumab on lung cancer among current as compared to past smokers (HR 0.50, P=0.005 for current smokers; HR 0.61, P=0.006 for past smokers). In the CANTOS trial specifically current smoker is defined as someone who smoked within the last 30 days at the time of screening. The definition of past smoker is someone who smoked in the past but not within the last 30 days at the time of screening.

[0076] Accordingly, in one embodiment, the subject is a smoker. In one further embodiment, the subject is a past smoker. In one embodiment, the present invention provides an IL-1 binding antibody or a functional fragment thereof for use in the treatment and/or prevention of lung cancer, wherein the incidence rate for lung cancer is reduced by at least 30%, at least 40% or at least 50% for smokers as compared to smokers not receiving such treatment.

[0077] In one embodiment, the subject is a male patient with lung cancer. In one embodiment said male patient is a current or past smoker.

[0078] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, gevokizumab or a functional fragment thereof, in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, in a patient who has a higher than normal level of C-reactive protein (hsCRP). In one further embodiment, this patient is a smoker. In one further embodiment, this patient is a current smoker. Typically cancers that have at least a partial inflammatory basis include but is not limited lung cancer, especially NSCLC, colorectal cancer (CRC), melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma, acute myeloblastic leukemia (AML), and biliary tract cancer.

[0079] A higher than normal level of C-reactive protein (hsCRP) has been particularly reported in, including but not being limited to, lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0080] As used herein, "C-reactive protein" and "CRP" refers to serum or plasma C-reactive protein, which is typically used as an indicator of the acute phase response to inflammation. Nonetheless, CRP level may become elevated in chronic illnesses such as cancer. The level of CRP in serum or plasma may be given in any concentration, e.g., mg/dl, mg/L, nmol/L. Levels of CRP may be measured by a variety of well known methods, e.g., radial immunodiffusion, electroimmunoassay, immunoturbidimetry (e.g., particle (e.g., latex)-enhanced turbidimetric immunoassay), ELISA, turbidimetric methods, fluorescence polarization immunoassay, and laser nephelometry. Testing for CRP may employ a standard CRP test or a high sensitivity CRP (hsCRP) test (i.e., a high sensitivity test that is capable of measuring lower levels of CRP in a sample, e.g., using immunoassay or laser nephelometry). Kits for detecting levels of CRP may be purchased from various companies. e.g., Calbiotech, Inc, Cayman Chemical, Roche Diagnostics Corporation, Abazyme, DADE Behring, Abnova Corporation, Aniara Corporation, Bio-Quant Inc., Siemens Healthcare Diagnostics, Abbott Laboratories etc.

[0081] As used herein, the term "hsCRP" refers to the level of CRP in the blood (serum or plasma) as measured by high sensitivity CRP testing. For example, Tina-quant C-reactive protein (latex) high sensitivity assay (Roche Diagnostics Corporation) may be used for quantification of the hsCRP level of a subject. Such latex-enhanced turbidimetric immunoassay may be analysed on the Cobas® platform (Roche Diagnostics Corporation) or Roche/Hitachi (e.g. Modular P) analyzer. In the CANTOS trial the hsCRP level was measured by Tina-quant C-reactive protein (latex) high sensitivity assay (Roche Diagnostics Corporation) on the Roche/Hitachi Modular P analyzer, which can be used typically and preferably as the method in measuring hsCRP level. Alternatively the hsCRP level can be measured by another method, for example by another approved companion diagnostic kit, the value of which can be calibrated against the value measured by the Tina-quant method.

[0082] Each local laboratory employ a cutoff value for abnormal (high) CRP or hsCRP based on that laboratory's rule for calculating normal maximum CRP, i.e. based on that laboratory's reference standard. A physician generally orders a CRP test from a local laboratory, and the local laboratory determines CRP or hsCRP value and reports normal or abnormal (low or high) CRP using the rule that particular laboratory employs to calculate normal CRP, namely based on its reference standard. Thus whether a patient has a higher than normal level of C-reactive protein (hsCRP) can be determined by the local laboratory where the test is conducted.

[0083] The present invention has shown for the first time in a clinical setting with the tested dosing range, that canakinumab is effective in hazard reduction of total lung cancer and fatal lung cancer. The effect is most pronounced in the cohort allocated to the highest canakinumab dose (300 mg twice over a two-week period and then every 3 months).

[0084] Furthermore, the present invention has shown for the first time in a clinical setting that an IL-1β antibody, canakinumab, is effective in reducing hsCRP level and the reduction of hsCRP is linked to effects in treating and/or preventing lung cancer. Hence it is plausible that an IL-1β antibody or a fragment thereof, such as canakinumab or gevokizumab, is effective in treating and/or preventing other cancer having at least partially inflammatory basis in a patient, especially when said patient has higher than normal level of hsCRP.

[0085] Furthermore, the present invention provides effective dosing ranges, within which the HsCRP level can be reduced to certain threshold, below which more patients with cancer having at least partially inflammatory basis can become responder or below which the same patient can benefit more from the great therapeutic effect of the Drug of the invention with negligible or tolerable side effects.

[0086] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment and/or prevention of cancer that has at least a partial inflammatory basis, including lung cancer, in a patient who has high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, equal to or higher than 3 mg/L, equal to or higher than 4 mg/L, equal to or higher than 5 mg/L, equal to or higher than 6 mg/L, equal to or higher than 7 mg/L, equal to or higher than 8 mg/L, equal to or higher than 9 mg/L, equal to or higher than 10 mg/L, equal to or higher than 12 mg/L, equal to or higher than 15 mg/L, equal to or higher than 20 mg/L or equal to or higher than 25 mg/L, preferably before first administration of said IL-1β binding antibody or functional fragment thereof. Preferably said patient has a hsCRP level equal to or higher than 4 mg/L. Preferably said patient has a hsCRP level equal to or higher than 6 mg/L. Preferably said patient has a hsCRP level equal to or higher than 10 mg/L. Preferably said patient has a hsCRP level equal to or higher than 20 mg/L. In one further embodiment, this patient is a smoker. In one further embodiment, this patient is a current smoker.

[0087] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of cancer that has at least a partial inflammatory basis in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention. In a preferred embodiment cancer that has at least a partial inflammatory basis is selected from a list consisting of lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer. AML, multiple myeloma and pancreatic cancer.

[0088] In one embodiment, the present invention provides the use of an IL-1B binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of CRC in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0089] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of RCC in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0090] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of pancreatic cancer in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0091] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of melanoma in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0092] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of HCC in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0093] In one embodiment, the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for the treatment of gastric cancer (including esophageal cancer), in a patient who has a high sensitivity C-reactive protein (hsCRP) level equal to or higher than 2 mg/L, higher than 6 mg/L, equal to or higher than 10 mg/L or equal to or higher than 20 mg/L, preferably before first administration of DRUG of the invention.

[0094] In one embodiment, the present invention provide the use of an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab, in the treatment and/or prevention of lung cancer in a patient, wherein said patient has atherosclerosis.

[0095] In one embodiment, the present invention provide the use of canakinumab in the treatment and/or prevention of lung cancer in a patient, wherein said patient has suffered from a qualifying CV event.

[0096] As used herein, the term "qualifying CV event" is selected from the group comprising myocardial infarction (MI), stroke, unstable angina, revascularization, stent thrombosis, acute coronary syndrome or any other CV event (excluding cardiovascular death) which precedes the start of IL-1β binding antibody or functional fragment thereof therapy.

[0097] In one embodiment, the present invention provide the use of canakinumab in the treatment and/or prevention of lung cancer in a patient, wherein said patient has suffered from a previous myocardial infarction. In a further embodiment, said patient is a stable post-myocardial infarction patient.

[0098] IL-1β inhibitors include but not be limited to canakinumab or a functional fragment thereof, gevokizumab or a functional fragment thereof, Anakinra, diacerein, Rilonacept, IL-1 Affibody (SOBI 006, Z-FC (Swedish Orphan Biovitrum/Affibody)) and Lutikizumab (ABT-981) (Abbott), CDP-484 (Celltech), LY-2189102 (Lilly).

[0099] In one embodiment of any use or method of the invention, said IL-1β binding antibody is canakinumab. Canakinumab (ACZ885) is a high-affinity, fully human monoclonal antibody of the IgG1/k to interleukin-1β, developed for the treatment of IL-1β driven inflammatory diseases. It is designed to bind to human IL-1 and thus blocks the interaction of this cytokine with its receptors. Canakinumab is disclosed in WO02/16436 which is hereby incorporated by reference in its entirety.

[0100] In other embodiments of any use or method of the invention, said IL-1β binding antibody is gevokizumab. Gevokizumab (XOMA-052) is a high-affinity, humanized monoclonal antibody of the IgG2 isotype to interleukin-1β, developed for the treatment of IL-1β driven inflammatory diseases. Gevokizumab modulates IL-1β binding to its signaling receptor. Gevokizumab is disclosed in WO2007/002261 which is hereby incorporated by reference in its entirety.

[0101] In one embodiment said IL-1β binding antibody is LY-2189102, which is a humanised interleukin-1 beta (IL-1β) monoclonal antibody.

[0102] In one embodiment said IL-1β binding antibody or a functional fragment thereof is CDP-484 (Celltech), which is an antibody fragment blocking IL-1β.

[0103] In one embodiment said IL-1β binding antibody or a functional fragment thereof is IL-1 Affibody (SOBI 006, Z-FC (Swedish Orphan Biovitrum/Affibody)).

[0104] In one embodiment said IL-1β binding antibody or a functional fragment thereof is Lutikizumab (ABT-981) (Abbott), which is a dual-variable domain antibody targeting interleukin 1 alpha (IL-1α) and interleukin 1 beta (IL-1β).

[0105] The present invention has shown for the first time in a clinical setting that an IL-1β antibody, canakinumab, is effective in reducing hsCRP level and the reduction of hsCRP is linked to effects in treating and/or preventing lung cancer. If an IL-1β inhibitor, such as an IL-1β antibody or a functional fragment thereof, is administered in a dose range that can effectively reduce hsCRP level in a patient with cancer having at least partial inflammatory basis, treatment effect of said cancer can possibly be achieved. Dose range, of a particular IL-1β inhibitor, preferably IL-1β antibody or a functional fragment thereof, that can effectively reduce hsCRP level is known or can be tested in a clinical setting.

[0106] Thus in one embodiment, the present invention comprises administering the IL-1β binding antibody or a functional fragment thereof to a patient with a cancer that has at least a partial inflammatory basis, including lung cancer, in the range of about 30 mg to about 750 mg per treatment, preferably in the range of about 60 mg to about 400 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, preferably 150 mg to 300 mg per treatment; alternatively about 90 mg to about 300 mg, or about 90 mg to about 200 mg per treatment, alternatively at least 150 mg, at least 180 mg, at least 300 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with a cancer that has at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every three weeks, every four weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). The term "per treatment", as used in this application and particularly in this context, should be understood as the total amount of drug received per hospital visit or per self administration or per administration helped by a health care giver. Normally and preferably the total amount of drug received per treatment is administered to a patient within one day, preferably within half a day, preferably within 4 hours, preferably within 2 hours. Typically cancers that have at least a partial inflammatory basis include but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0107] In one preferred embodiment patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives a dose of about 90 mg to about 450 mg of the IL-1 binding antibody or a functional fragment thereof per treatment. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives DRUG of the invention monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives DRUG of the invention every three week. In one embodiment the patient with lung cancer receives DRUG of the invention monthly. In one embodiment the patient with lung cancer receives DRUG of the invention every three week. In one embodiment the range of DRUG of the invention is at least 150 mg or at least 200 mg. In one embodiment the range of DRUG of the invention is 180 mg to 450 mg.

[0108] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is colorectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is RCC. In one embodiment said cancer is melanoma. In one embodiment said cancer is pancreatic cancer.

[0109] In practice some times the time interval can not be strictly kept due to the limitation of the availability of doctor, patient or the drug/facility. Thus the time interval can slightly vary, normally between ±5 days, ±4 days, ±3 days, ±2 days or preferably 1 day.

[0110] In one embodiment, the present invention comprises administering the IL-1 binding antibody or a functional fragment thereof to a patient with a cancer having at least a partial inflammatory basis, including lung cancer, in a total dose of from 100 mg to about 750 mg, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively in a total dose of from 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, alternatively in a total dose of at least 150 mg, at least 180 mg, at least 250 mg, at least 300 mg, over a period of 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks or 12 weeks, preferably 4 weeks. In one embodiment total dose of DRUG of the invention is 180 mg to 450 mg.

[0111] In one embodiment, the total dose of the DRUG of the invention is administered multiple times, preferably 2, 3 or 4 times over the above defined period. In one embodiment, DRUG of the invention is administered once over the above defined period.

[0112] Some times it is desirable to quickly reduce inflammation of patients diagnosed with cancer having at least

partially inflammatory basis, including lung cancer. IL-1 auto-induction has been shown in human mononuclear blood, human vascular endothelial, and vascular smooth muscle cells in vitro and in rabbits in vivo where IL-1 has been shown to induce its own gene expression and circulating IL-1βp level (Dinarello et al. 1987, Warner et al. 1987a, and Warner et al. 1987b).

[0113] This induction period over 2 weeks by administration of a first dose followed by a second dose two weeks after administration of the first dose is to assure that auto-induction of IL-1β pathway is adequately inhibited at initiation of treatment. The complete suppression of IL-1β related gene expression achieved with this early high dose administration, coupled with the continuous canakinumab treatment effect which has been proven to last the entire quarterly dosing period used in CANTOS, is to minimize the potential for IL-1β rebound. In addition, data in the setting of acute inflammation suggests that higher initial doses of canakinumab that can be achieved through induction are safe and provide an opportunity to ameliorate concern regarding potential auto-induction of IL-1β and to achieve greater early suppression of IL-1β related gene expression.

[0114] Thus in one embodiment, the present invention, while keeping the above described dosing schedules, especially envisages the second administration of DRUG of the invention is at most two weeks, preferably two weeks apart from the first administration. Then the third and the further administration will following the schedule of every 2 weeks, every 3 weeks, every 4 weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months).

[0115] In one embodiment, the IL-1 binding antibody is canakinumab, wherein canakinumab is administered to a patient with cancer having at least a partial inflammatory basis, including lung cancer, in the range of about 100 mg to about 750 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg per treatment, alternatively about 200 mg to 400 mg, 200 mg to 300 mg, alternatively at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with cancer having at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every 3 weeks, every 4 weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). Typically cancer having at least a partial inflammatory basis includes but not be limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer. In one embodiment the patient with lung cancer receives canakinumab monthly or every three weeks. In one embodiment the preferred dose range of canakinumab is 200 mg to 450 mg, further preferred 300 mg to 450 mg, further preferred 350 mg to 450 mg per treatment. In one embodiment the preferred dose range of canakinumab for patient with lung cancer is 200 mg to 450 mg every 3 weeks or monthly. In one embodiment the preferred dose of canakinumab for patient with lung cancer is 200 mg every 3 weeks. In one embodiment the preferred dose of canakinumab for patient with lung cancer is 200 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives canakinumab monthly or every three week. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives canakinumab in the dose range of 200 mg to 450 mg monthly or every three week. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives canakinumab at a dose of 200 mg monthly or every three weeks.

[0116] Suitable the above dose and dosing apply to the use of a functional fragment of canakinumab according to the present invention.

[0117] In one embodiment, the present invention comprises administering canakinumab to a patient with cancer that has at least a partial inflammatory basis, including lung cancer, in a total dose of from 100 mg to about 750 mg, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, preferably 150 mg to 300 mg, preferably 300 mg to 450 mg; alternatively at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg, preferably at least 300 mg, over a period of 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks or 12 weeks, preferably 4 weeks. In one embodiment, canakinumab is administered multiple times, preferably 2, 3 or 4 times over the above defined period. In one embodiment, canakinumab is administered once over the above defined period. In one embodiment the preferred total dose of canakinumab is 200 mg to 450 mg, further preferred 300 mg to 450 mg, further preferred 350 mg to 450 mg.

[0118] In one embodiment, the present invention, while keeping the above described dosing schedules, especially envisages the second administration of canakinumab is at most two weeks, preferably two weeks apart from the first administration.

[0119] In one embodiment, the present invention comprises administering canakinumab at a dose of 150 mg every 2 weeks, every 3 weeks or monthly.

[0120] In one embodiment, the present invention comprises administering canakinumab at a dose of 300 mg every 2 weeks, every 3 weeks, monthly, every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months).

[0121] In one embodiment, the present invention comprises administering canakinumab at a dose of 300 mg once per month (monthly). In one further embodiment, the present invention, while keeping the above described dosing schedules, especially envisages the second administration of canakinumab at 300 mg is at most two weeks, preferably two weeks apart from the first administration.

[0122] In one embodiment of the invention, canakinumab is administered to a patient in need at 300 mg twice over a two week period and then every 3 month.

[0123] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is correlectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0124] In one embodiment, the present invention comprises administering gevokizumab to a patient with cancer that has at least a partial inflammatory basis, including lung cancer, in the range of about 30 mg to about 450 mg per treatment, alternatively 90 mg-450 mg, 90 mg to 360 mg, 90 mg to 270 mg, 90 mg to 180 mg per treatment; alternatively 120 mg-450 mg, 120 mg to 360 mg, 120 mg to 270 mg, 120 mg to 180 mg per treatment, alternatively 150 mg-450 mg, 150 mg to 360 mg, 150 mg to 270 mg, 150 mg to 180 mg per treatment, alternatively 180 mg-450 mg, 180 mg to 360

mg, 180 mg to 270 mg per treatment; alternatively about 60 mg to about 360 mg, about 60 mg to 180 mg per treatment, alternatively at least 150 mg, at least 180 mg, at least 240 mg, at least 270 mg per treatment. In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives treatment every 2 weeks, every 3 weeks, monthly (every 4 weeks), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives at least one, preferably one treatment per month. Typically cancers that have at least a partial inflammator-basis include but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer. AML, multiple myeloma and pancreatic cancer. In one embodiment the preferred range of gevokizumab is 150 mg to 270 mg. In one embodiment the preferred range of gevokizumab is 60 mg to 180 mg, further preferred 60 mg to 90 mg. In one embodiment the preferred range of gevokizumab is 90 mg to 270 mg, further preferred 90 mg to 180 mg. In one embodiment the preferred schedule is every 3 weeks or monthly. In one embodiment the patient receives gevokizumab 60 mg to 90 mg every 3 weeks. In one embodiment the patient receives gevokizumab 60 mg to 90 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg every 3 weeks. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg monthly.

[0125] In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 120 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 120 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 90 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 180 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 180 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 200 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 200 mg monthly.

[0126] Suitable the above dose and dosing apply to the use of a functional fragment of gevokizumab according to the present invention.

[0127] In one embodiment, the present invention comprises administering gevokizumab to a patient with lung cancer in a total dose of 90 mg-450 mg, 90 mg to 360 mg, 90 mg to 270 mg, 90 mg to 180 mg, alternatively 120 mg-450 mg, 120 mg to 360 mg, 120 mg to 270 mg, 120 mg to 180 mg, alternatively 150 mg-450 mg, 150 mg to 360 mg, 150 mg to 270 mg, 150 mg to 180 mg, alternatively 180 mg-450 mg, 180 mg to 360 mg, 180 mg to 270 mg, alternatively at least 90 mg, at least 120 mg, at least 150 mg, at least 180 mg over a period of 2 weeks, 3 weeks, 4 weeks, 6 weeks, 8 weeks or 12 weeks, preferably 4 weeks. In one embodiment, gevokizumab is administered multiple times, preferably 2, 3 or 4 times over the above defined period. In one embodiment, gevokizumab is administered once over the above defined period. In one embodiment the preferred total dose of gevokizumab is 180 mg to 360 mg. In one embodiment, the patient with lung cancer receives gevokizumab at least one, preferably one treatment per month.

[0128] In one embodiment, the present invention, while keeping the above described dosing schedules, especially envisages the second administration of gevokizumab is at most two weeks, preferably two weeks apart from the first administration.

[0129] In one embodiment, the present invention comprises administering gevokizumab at a dose of 60 mg every 2 weeks, every 3 weeks or monthly.

[0130] In one embodiment, the present invention comprises administering gevokizumab at a dose of 90 mg every 2 weeks, every 3 weeks or monthly.

[0131] In one embodiment, the present invention comprises administering gevokizumab at a dose of 180 mg every 2 weeks, every 3 weeks (±3 days), monthly, every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months).

[0132] In one embodiment, the present invention comprises administering gevokizumab at a dose of 180 mg once per month (monthly). In one further embodiment, the present invention, while keeping the above described dosing schedules, envisages the second administration of gevokizumab at 180 mg is at most two weeks, preferably two weeks apart from the first administration.

[0133] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is colorectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0134] In one embodiment, the present invention provides an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab, for use in the treatment and/or prevention of cancer that has at least a partial inflammatory basis, including lung cancer, wherein the risk for cancer that has at least a partial inflammatory basis, including lung cancer, is reduced by at least 30%, at least 40%, at least 50% at 3 months from the first administration compared to patient not receiving the treatment. In one preferred embodiment, the dose of the first administration is at 300 mg. In one further preferred embodiment, the dose of the first administration is at 300 mg followed by a second dose of 300 mg within a two-week period. Preferably the result is achieved with a dose of 200 mg canakinumab administered every 3 weeks. Preferably the result is achieved with a dose of 200 mg canakinumab administered every month.

[0135] In one embodiment, the present invention provides an IL-1β binding antibody or functional fragment thereof, suitably canakinumab, for use in the treatment and/or prevention of cancer that has at least a partial inflammatory basis, including lung cancer, wherein the risk for lung cancer mortality is reduced by at least 30%, at least 40% or at least 50% compared to a patient not receiving the treatment. Preferably the results is achieved at a dose of 200 mg canakinumab administered every 3 weeks or 300 mg canakinumab administered monthly, preferably for at least for one year, preferably up to 3 years.

[0136] In one embodiment, the present invention provides an IL-1β binding antibody or functional fragment thereof,

suitably canakinumab, for use in the treatment and/or prevention of lung cancer, wherein the incident rate for adenocarcinoma or poorly differentiated large cell carcinoma is reduced by at least 30%, at least 40%0/or at least 50% compared to patient not receiving such treatment. Preferably the results is achieved at a dose of 300 mg of canakinumab monthly administration or preferably at a dose of 200 mg canakinumab administered every 3 weeks or monthly, preferably for at least for one year, preferably up to 3 years.

[0137] In one embodiment, the present invention provides an IL-1β binding antibody or functional fragment thereof, suitably canakinumab, for use in the treatment and/or prevention of cancer, wherein the risk for total cancer mortality is reduced by at least 30%, at least 40%6, or at least 50% compared to a patient not receiving such treatment. Preferably the results is achieved at a dose of 300 mg or 200 mg canakinumab administered monthly or preferably at a dose of 200 mg canakinumab administered every 3 weeks, preferably subcutaneously, preferably for at least for one year, preferably up to 3 years.

[0138] In one embodiment, the present invention provides an IL-1β binding antibody or functional fragment thereof, suitably canakinumab or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof for use, in the treatment of cancer that has at least a partial inflammatory basis, wherein the risk for said cancer mortality is reduced by at least 30%, at least 40% or at least 50% compared to a patient not receiving the treatment. Preferably the results is achieved at a dose of 200 mg canakinumab administered every 3 weeks or monthly, preferably for at least for one year, preferably up to 3 years. Preferably the results is achieved at a dose of 120 mg gevokizumab administered every 3 weeks or monthly, preferably for at least for one year, preferably up to 3 years. Preferably the results is achieved at a dose of 90 mg gevokizumab administered every 3 weeks or monthly, preferably for at least for one year, preferably up to 3 years.

[0139] In one embodiment, the present invention provides canakinumab for use in the treatment and/or prevention of lung cancer, wherein the effects were dose dependent with relative hazard reductions of 67% and 77% for total lung cancer and fatal lung cancer, respectively, among those randomly allocated to the highest canakinumab dose (300 mg twice over a two-week period and then every 3 months).

[0140] In one embodiment, the present invention provides canakinumab for use in the treatment and/or prevention of lung cancer, wherein beneficial effects of canakinumab are observed on incident lung cancers within weeks from the first administration. In one preferred embodiment, the dose of the first administration is at 300 mg. In one further preferred embodiment, the dose of the first administration is at 300 mg followed by a second dose of 300 mg within a two-week period. In one further preferred embodiment, a dose of 200 mg canakinumab is administered every three weeks or monthly.

[0141] In one aspect the present invention provides an IL-1 binding antibody or a functional fragment thereof for use in the treatment of cancer having at least a partial inflammatory basis, including lung cancer, especially NSCLC, in a patient, wherein the efficacy of the treatment correlates with the reduction of hsCRP in said patient, comparing to prior treatment. In one embodiment the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment of cancer having at least a partial inflammatory basis, including lung cancer, especially NSCLC, in a patient, wherein the CRP level, more precisely the hsCRP level, of said patient has reduced to below 15 mg/L, below 10 mg/L, preferably to below 6 mg/L, preferably to below 4 mg/L, preferably to below 3 mg/L, preferably to below 2.3 mg/L, preferably to below 2 mg/L, to below 1.8 mg/L, about 6 months, or preferably about 3 months from the first administration of said IL-1β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention. Typically cancers that have at least a partial inflammatory basis include but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0142] In one embodiment, said IL-1β binding antibody is canakinumab or a functional fragment thereof. In one preferred embodiment, the proper dose of the first administration of canakinumab is 300 mg. In one preferred embodiment, canakinumab is administered at a dose of 300 mg monthly. In one preferred embodiment, canakinumab is administered at a dose of 300 mg monthly with an additional dose at 2 weeks interval from the first administration. In one preferred embodiment, canakinumab is administered at a dose of 200 mg. In one preferred embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly. In one preferred embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly subcutaneously.

[0143] In one embodiment, said IL-1β binding antibody is gevokizumab or a functional fragment thereof. In one preferred embodiment, the proper dose of the first administration of gevokizumab is 180 mg. In one preferred embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg. In one preferred embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg every 3 weeks or monthly. In one preferred embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or every 4 weeks (monthly). In one preferred embodiment, gevokizumab is administered intravenously. In one preferred embodiment, gevokizumab is administered at a dose of 90 mg every 3 weeks or every 4 weeks (monthly) intravenously. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 120 mg every 3 weeks. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 180 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 180 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 200 mg every 3 weeks. In one embodiment the patient receives gevokizumab about 200 mg monthly. Gevokizumab is administered subcutaneously or preferably introvenously.

[0144] Further preferably the hsCRP level, of said patient has reduced to below 10 mg/L, preferably to below 6 mg/L, preferably to below 4 mg/L, preferably to below 3 mg/L, preferably to below 2.3 mg/L, preferably to below 2 mg/L, to below 1.8 mg/L, after the first administration of the DRUG of the invention according to the dose regimen of the present invention. In one preferred embodiment, the proper dose of the first administration of canakinumab is at least 150 mg, preferably at least 200 mg. In one preferred

embodiment, the proper dose of the first administration of gevokizumab is 90 mg. In one preferred embodiment, the proper dose of the first administration of gevokizumab is 120 mg. In one preferred embodiment, the proper dose of the first administration of gevokizumab is 180 mg. In one preferred embodiment, the proper dose of the first administration of gevokizumab is 200 mg.

[0145] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is colorectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0146] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment of cancers that have at least a partial inflammatory basis, including lung cancer, especially NSCLC, in a patient, wherein the hsCRP level of said patient has reduced by at least 15%, at least 20%, at least 30% or at least 40% 6 months, or preferably 3 month from the first administration of said IL-1β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention, as compared to the hsCRP level just prior to the first administration of the IL-1β binding antibody or a functional fragment thereof. Further preferably the hsCRP level of said patient has reduced by at least 15%, at least 20%, at least 30% after the first administration of the DRUG of the invention according to the dose regimen of the present invention.

[0147] In one aspect the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment of cancers that have at least a partial inflammatory basis, including lung cancer, especially NSCLC, in a patient, wherein the IL-6 level of said patient has reduced by at least 15%, at least 20%, at least 30% or at least 40% about 6 months, or preferably about 3 months from the first administration of said IL-1β binding antibody or a functional fragment thereof at a proper dose, preferably according to the dosing regimen of the present invention, as compared to the IL-6 level just prior to the first administration. The term "about" used herein includes a variation of ±10 days from the 3 months or a variation of ±15 days from the 6 months. Typically cancers that have at least a partial inflammatory basis include but not be limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer. In one embodiment, said IL-1β binding antibody is canakinumab or a functional fragment thereof. In one preferred embodiment, the proper dose of the first administration of canakinumab is 300 mg. In one preferred embodiment, canakinumab is administered at a dose of 300 mg monthly. In one preferred embodiment, canakinumab is administered at a dose of 300 mg monthly with an additional dose at 2 weeks from the first administration. In one preferred embodiment, canakinumab is administered at a dose of 200 mg. In one preferred embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly. In one preferred embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly subcutaneously. In another embodiment, said IL-1β binding antibody is gevokizumab or a functional fragment thereof. In one preferred embodiment, the proper dose of the first administration of gevokizumab is 180 mg. In one preferred embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg. In one preferred embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg every 3 weeks or monthly. In one preferred embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or every 4 weeks (monthly). In one preferred embodiment, gevokizumab is administered intravenously. In one preferred embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or every 4 weeks (monthly) intravenously. In one preferred embodiment, gevokizumab is administered at a dose of 90 mg every 3 weeks or every 4 weeks (monthly) intravenously.

[0148] The reduction of the level of hsCRP and the reduction of the level of IL-6 can be used separately or in combination to indicate the efficacy of the treatment or as prognostic markers.

[0149] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is correlectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0150] In one aspect, the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment and/or prevention of cancers that have at least a partial inflammatory basis, including lung cancer, especially NSCLC, in a patient with a high sensitive C-reactive protein (hsCRP) of ≥22 mg/L, wherein the antibody is canakinumab and the patient experiences a reduced chance of death from cancer over at least a five year period. In one further embodiment the patient has at least a 51% reduced chance of death from cancer over at least a five year period.

[0151] In one aspect the present invention provides the use of an IL-1β binding antibody or a functional fragment thereof in the prevention of lung cancer in a patient. The term "prevent", "preventing" or "prevention" as used herein means the prevention or delay the occurrence of lung cancer in a subject who is otherwise at high risk of developing lung cancer. In one preferred embodiment, canakinumab is administered at a dose of 200 mg. In one preferred embodiment, canakinumab is administered at a dose of 100 mg to 200 mg, preferably 200 mg, every three weeks, monthly, every 6 weeks, even other month or quarterly, preferably subcutaneously. In another embodiment, said IL-1β binding antibody is gevokizumab or a functional fragment thereof. In one preferred embodiment, gevokizumab is administered at a dose of 30 mg to 90 mg. In one preferred embodiment, gevokizumab is administered at a dose of 30 mg to 90 mg every three weeks, monthly, every 6 weeks, every other month or quarterly. In one preferred embodiment, gevokizumab is administered at a dose of 60 mg to 120 mg every three weeks, monthly, every 6 weeks, every other month or quarterly, preferably intravenously. In one preferred embodiment, gevokizumab is administered at a dose of 90 mg every three weeks, monthly, every 6 weeks, every other month or quarterly, preferably intravenously. In one preferred embodiment, gevokizumab is administered at a dose of 120 mg every three weeks, monthly, every 6 weeks, every other month or quarterly, preferably subcutaneously.

[0152] Risk factors include but are not limited to age, genetic mutation, smoking, long term exposure to inhalable hazards, for example due to profession, etc.

[0153] In one embodiment said patient is over 60 years old, over 62 years old or over 65 years or over 70 years old. In one embodiment, said patient is a male. In another embodiment, said patient is female. In one embodiment said patient is a smoker, especially a current smoker. Smoker can be understood, more broadly than the definition of the CANTOS trial, as someone who smokes more than 5 cigarettes a day (current smoker) or someone who has a smoking history (past smoker). Normally the smoking history is in total more than 5 years or more than 10 years. Normally during the smoking period more than 10 cigarettes or more than 20 cigarettes were smoked per day.

[0154] In one embodiment said patient has chronic bronchitis. In one embodiment said patient was exposed or has been exposed or is being exposed for long period (more than 5 years or even more than 10 years), for example due to profession, to external inhaled toxins, such as asbestos, silica, smoking, and other external inhaled toxins. If a patient has the above mentioned one, or the combination of any of the two, any of the three, any of the four, any of the five or any of the six conditions, such patient is likely to have higher likelihood of developing lung cancer. The present invention envisages the use of an IL-1β binding antibody or functional fragment thereof, suitably canakinumab or a functional fragment thereof, or gevokizumab or a functional fragment thereof, in the prevention of lung cancer in such a patient. In one preferred embodiment, such a male patient is over 65, or over 70 years old who is a smoker. In one embodiment, such a male patient is over 65 years of age, or over 70 years of age who is a current or past smoker. In one embodiment, such a female patient is over 65 years of age, or over 70 years of age who is a smoker. In one further embodiment, said patient smokes or had smoked in the past more than 10, more than 20 cigarettes or more than 30 cigarettes or more than 40 cigarettes per day.

[0155] In one embodiment, the present invention provides an IL-1 binding antibody or a functional fragment thereof, suitably canakinumab, or a functional fragment thereof, or gevokizumab, or a functional fragment thereof, for use in the prevention of lung cancer in a subject with a high sensitive C-reactive protein (hsCRP) equal to or higher than 2 mg/L, or equal to or higher than 3 mg/L, or equal to or higher than 4 mg/L, or equal to or higher than 5 mg/L, equal to or higher than 6 mg/L, equal to or higher than 8 mg/L, equal to or higher than 9 mg/L, or equal to or higher than 10 mg/L as assessed prior to the administration of the IL-1β binding antibody or functional fragment thereof. In one preferred embodiment, said subject has hsCRP level equal to or higher than 6 mg/L as assessed prior to the administration of the IL-1β binding antibody or functional fragment thereof. In one preferred embodiment, said subject had hsCRP level equal to or higher than 10 mg/L as assessed prior to the administration of the IL-1 binding antibody or functional fragment thereof. In one embodiment, said an IL-1β binding antibody is canakinumab or a functional fragment thereof, or gevokizumab or a functional fragment thereof. In one further embodiment, said subject is a smoker. In one further embodiment said subject is over 65 years old. In one further embodiment said subject has inhaled toxins, such as asbestos, silica or smoking for more than 10 years.

[0156] In one embodiment, the present invention provides an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, or gevokizumab or a functional fragment thereof, for use in the prevention of recurrence or relapse of cancer having at least a partial inflammatory basis, including lung cancer, in a subject, wherein said subject had cancer or lung cancer, which has been surgically removed (resected). Typically cancers that have at least a partial inflammatory basis include but not be limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, multiple myeloma and pancreatic cancer. In a preferred embodiment said patient has completed post-surgery standard chemotherapy (other than the treatment of DRUG of the invention) treatment and/or completed standard radiotherapy treatment. The term post-surgery standard chemotherapy including standard small molecule chemotherapeutic agents and/or antibodies, particularly check point inhibitors. In one further preferred embodiment, canakinumab or gevokizumab is administered as monotherapy in the prevention of recurrence or relapse of cancer having at least a partial inflammatory basis, including lung cancer. In one embodiment, canakinumab or gevokizumab is administered to said patient post-surgery in combination with radiotherapy or in combination with chemotherapy, particularly standard chemotherapy. In one embodiment, canakinumab is administered every month at a dose of 200 mg, particularly when administered as monotherapy, preferably subcutaneously. In one embodiment, canakinumab is administered every 3 weeks or monthly at a dose of 200 mg, particularly when administered in combination with chemotherapy, particularly standard of care chemotherapy, particular in combination with a checkpoint inhibitor, such as a PD-1 or PD-L1 inhibitor, preferably subcutaneously. In one embodiment, gevokizumab is administered every month at a dose of 60 mg to 180 mg, every month at a dose of 90 mg to 120 mg, or 60 mg to 90 mg, preferably 120 mg, particularly when administered as monotherapy in the prevention of recurrence or relapse of cancer having at least a partial inflammatory basis, including lung cancer or colorectal cancer, RCC or gastric cancer, preferably intravenously. In one embodiment, gevokizumab is administered every 3 weeks at a dose of 60 mg to 180 mg, 90 mg to 120 mg or 60 mg to 90 mg, preferably 120 mg, particularly when administered in combination with chemotherapy, particularly standard chemotherapy, particular in combination with a checkpoint inhibitor, such as a PD-1 or PD-L1 inhibitor, preferably intravenously.

[0157] In one embodiment said cancer having at least a partial inflammatory basis is breast cancer. In one embodiment said cancer is colorectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0158] In one embodiment, canakinumab is administered every 3 months at a dose of 50 mg-300 mg, 50-150 mg, 75 mg-150 mg, 100 mg-150 mg, 50 mg, 150 mg or 300 mg. In the aspect of prevention, canakinumab is administered to a patient in need thereof at a dose of 50 mg, 150 mg or 300 mg, preferably 150 mg, monthly, bimonthly or every 3 months. In one embodiment, canakinumab is administered

to a patient in need thereof for the prevention of lung cancer at a dose of 150 mg every 3 months.

[0159] In one embodiment said gevokizumab is administered every 3 months at a dose of 30 mg-180 mg, 30 mg-120 mg, 30 mg-90 mg, 60 mg-120 mg, 60 mg-90 mg, 30 mg, 60 mg, 90 mg or 180 mg.

[0160] In one embodiment, the IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, is administered to said patient with cancer having at least partial inflammatory basis prior to surgery (neoadjuvant chemotherapy) or post surgery (adjuvant chemotherapy). In one embodiment, IL-1β binding antibody or functional fragment thereof is administered to said patient prior to, concomitantly with or post radiotherapy.

[0161] In one aspect, the present invention provides an IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis, wherein said IL-1β binding antibody or a functional fragment thereof is administered in combination with one or more chemotherapeutic agents. Typically cancer having at least partial inflammatory basis include but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0162] In one embodiment the IL-1β binding antibody or a functional fragment thereof, suitably canakinumab or gevokizumab, is administered in combination with one or more chemotherapeutic agents.

[0163] Without wishing being bound by the theory, it is believed that typical cancer development requires two steps. Firstly gene alteration results in cell growth and proliferation no longer subject to regulation. Secondly the abnormal tumor cells evade surveillance of the immune system. Inflammation plays important role in the second step. Therefore, control of inflammation, as supported for the first time by the clinical data from the CANTOS trial, can stop cancer development at the early or earlier stage. Thus it is expected that blocking IL-1β pathway to reduce inflammation would have a general benefit, particularly improvement of the treatment efficacy on top of the standard of care, which is mainly to directly inhibit the growth and proliferation of the malignant cells. In one embodiment the one or more chemotherapeutic agents is the standard of care agents of said cancer having at least partial inflammatory basis.

[0164] Check point inhibitors de-suppress the immune system through a mechanism different from IL-1β inhibitors. Thus the addition of IL-1β inhibitors, particularly IL-1β binding antibodies or a functional fragment thereof to the standard Check point inhibitors therapy will further active the immune response, particularly at the tumor microenvironment.

[0165] In one embodiment, the one or more chemotherapeutic agents is nivolumab and ipilimumab.

[0166] In one embodiment, the one or more chemotherapeutic agents is cabozantinib, or a pharmaceutically acceptable salt thereof.

[0167] In one embodiment the or more chemotherapeutic agent is Atezolizumab plus bevacizumab.

[0168] In one embodiment the one or more chemotherapeutic agent is FOLFIRI plus bevacizumab or FOLFOX plus bevacizumab.

[0169] Chemotherapeutic agents are cytotoxic and/or cytostatic drugs (drugs that kill malignant cells, or inhibit their proliferation, respectively) as well as check point inhibitors. Commonly known chemotherapeutic agent includes but is not limited to platinum agents (e.g., cisplatin, carboplatin, oxaliplatin, nedaplatin, triplatin, lipoplatin, satraplatin, picoplatin), antimetabolites (e.g., methotrexate, 5-Fluorouracil, gemcitabine, pemetrexed, edatrexate), mitotic inhibitors (e.g., paclitaxel, albumin-bound paclitaxel, docetaxel, taxotere, docecad), alkylating agents (e.g., cyclophosphamide, mechlorethamine hydrochloride, ifosfamide, melphalan, thiotepa), vinca alkaloids (e.g., vinblastine, vincristine, vindesine, vinorelbine), topoisomerase inhibitors (e.g., etoposide, teniposide, topotecan, irinotecan, camptothecin, doxorubicin), antitumor antibiotics (e.g., mitomycin C) and/or hormone-modulating agents (e.g., anastrozole, tamoxifen). Examples of anti-cancer agents used for chemotherapy include Cyclophosphamide (Cytoxan®), Methotrexate, 5-Fluorouracil (5-FU), Doxorubicin (Adriamycin®), Prednisone, Tamoxifen (Nolvadex®), Paclitaxel (Taxol®), Albumin-bound paclitaxel (nab-paclitaxel, Abraxane®), Leucovorin, Thiotepa (Thioplex®), Anastrozole (Arimidex®), Docetaxel (Taxotere®), Vinorelbine (Navelbine®), Gemcitabine (Gemzar®), Ifosfamide (Ifex®), Pemetrexed (Alimta®), Topotecan, Melphalan (L-Pam®), Cisplatin (Cisplatinum®, Platinol®), Carboplatin (Paraplatin®), Oxaliplatin (Eloxatin®), Nedaplatin (Aqupla®), Triplatin, Lipoplatin (Nanoplatin®). Satraplatin, Picoplatin, Carmustine (BCNU; BiCNU®), Methotrexate (Folex®, Mexate®), Edatrexate, Mitomycin C (Mutamycin®), Mitoxantrone (Novantrone®), Vincristine (Oncovin®), Vinblastine (Velban®), Vinorelbine (Navelbine®), Vindesine (Eldisine®), Fenretinide, Topotecan, Irinotecan (Camptosar®), 9-amino-camptothecin [9-AC], Biantrazole, Losoxantrone, Etoposide, and Teniposide.

[0170] In one embodiment, the preferred combination partner for the IL-1β binding antibody or a functional fragment thereof is a mitotic inhibitor, preferably docetaxel. In one embodiment, the preferred combination partner for canakinumab is a mitotic inhibitor, preferably docetaxel. In one embodiment, the preferred combination partner for gevokizumab is a mitotic inhibitor, preferably docetaxel. In one embodiment said combination is used for the treatment of lung cancer, especially NSCLC.

[0171] In one embodiment, the preferred combination partner for the IL-1β binding antibody or a functional fragment thereof is a platinum agent, preferably cisplatin. In one embodiment, the preferred combination partner for canakinumab is a platinum agent, preferably cisplatin. In one embodiment, the preferred combination partner for gevokizumab is a platinum agent, preferably cisplatin. In one embodiment, the one or more chemotherapeutic agent is a platinum-based doublet chemotherapy (PT-DC).

[0172] Chemotherapy may comprise the administration of a single anti-cancer agent (drug) or the administration of a combination of anti-cancer agents (drugs), for example, one of the following, commonly administered combinations of: carboplatin and taxol; gemcitabine and cisplatin; gemcitabine and vinorelbine; gemcitabine and paclitaxel; cisplatin and vinorelbine; cisplatin and gemcitabine; cisplatin and paclitaxel (Taxol); cisplatin and docetaxel (Taxotere); cis-

platin and etoposide; cisplatin and pemetrexed; carboplatin and vinorelbine; carboplatin and gemcitabine; carboplatin and paclitaxel (Taxol); carboplatin and docetaxel (Taxotere); carboplatin and etoposide; carboplatin and pemetrexed. In one embodiment, the one or more chemotherapeutic agent is a platinum-based doublet chemotherapy (PT-DC).

[0173] Another class of chemotherapeutic agents are the inhibitors, especially tyrosine kinase inhibitors, that specifically target growth promoting receptors, especially VEGF-R, EGFR, PFGF-R and ALK, or their downstream members of the signalling transduction pathway, the mutation or overproduction of which results in or contributes to the oncogenesis of the tumor at the site (targeted therapies). Exemplary of targeted therapies drugs approved by the Food and Drug administration (FDA) for the targeted treatment of lung cancer include but not limited bevacizumab (Avastin®), crizotinib (Xalkori®), erlotinib (Tarceva®), gefitinib (Iressa®), afatinib dimaleate (Gilotrif®), ceritinib (LDK378/Zykadia™), everolimus (Afinitor®), ramucirumab (Cyramza®), osimertinib (Tagrisso™), necitumumab (Portrazza™), alectinib (Alecensa®), atezolizumab (Tecentriq®), brigatinib (Alunbrig™), trametinib (Mekinist®), dabrafenib (Tafinlar®), sunitinib (Sutent®) and cetuximab (Erbitux®).

[0174] In one embodiment the one or more chemotherapeutic agent to be combined with the IL-1β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is the agent that is the standard of care agent for lung cancer, including NSCLC and SCLC. Standard of care, can be found, for example from American Society of Clinical Oncology (ASCO) guideline on the systemic treatment of patients with stage IV non-small-cell lung cancer (NSCLC) or American Society of Clinical Oncology (ASCO) guideline on Adjuvant Chemotherapy and Adjuvant Radiation Therapy for Stages I-IIIA Resectable Non-Small Cell Lung Cancer.

[0175] In one embodiment the one or more chemotherapeutic agent to be combined with the IL-1β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is a platinum containing agent or a platinum-based doublet chemotherapy (PT-DC). In one embodiment said combination is used for the treatment of lung cancer, especially NSCLC. In one embodiment one or more chemotherapeutic agent is a tyrosine kinase inhibitor. In one preferred embodiment said tyrosine kinase inhibitor is a VEGF pathway inhibitor or an EGF pathway inhibitor. In one embodiment said combination is used for the treatment of lung cancer, especially NSCLC.

[0176] In one embodiment the one or more chemotherapeutic agent to be combined with the IL-1β binding antibody or fragment thereof, suitably canakinumab or gevokizumab, is a check-point inhibitor. In one further embodiment, said check-point inhibitor is nivolumab or pembrolizumab. In one further embodiment, said check-point inhibitor is atezolizumab. In one further embodiment, said check-point inhibitor is PDR-001 (spartalizumab). In one embodiment, said check-point inhibitor is durvalumab. In one embodiment, said check-point inhibitor is avelumab. Immunotherapies that target immune checkpoints, also known as check-point inhibitors, are currently emerging as key agents in cancer therapy. The immune checkpoint inhibitor can be an inhibitor of the receptor or an inhibitor of the ligand. Examples of the inhibiting targets include but not limited to a co-inhibitory molecule (e.g., a PD-1 inhibitor (e.g., an anti-PD-1 antibody molecule), a PD-L1 inhibitor (e.g., an anti-PD-L 1 antibody molecule), a PD-L2 inhibitor (e.g., an anti-PD-L2 antibody molecule), a LAG-3 inhibitor (e.g., an anti-LAG-3 antibody molecule), a TIM-3 inhibitor (e.g. an anti-TIM-3 antibody molecule)), an activator of a co-stimulatory molecule (e.g., a GITR agonist (e.g., an anti-GITR antibody molecule)), a cytokine (e.g., IL-15 complexed with a soluble form of IL-15 receptor alpha (IL-15Ra)), an inhibitor of cytotoxic T-lymphocyte-associated protein 4 (e.g., an anti-CTLA-4 antibody molecule) or any combination thereof.

PD-1 Inhibitors In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with a PD-1 inhibitor. In one some embodiment the PD-1 inhibitor is chosen from PDR001 (spartalizumab) (Novartis), Nivolumab (Bristol-Myers Squibb), Pembrolizumab (Merck & Co), Pidilizumab (CureTech). MEDI0680 (Medimmune), REGN2810 (Regeneron), TSR-042 (Tesaro), PF-06801591 (Pfizer), BGB-A317 (Beigene), BGB-108 (Beigene), INCSHR1210 (Incyte), or AMP-224 (Amplimmune).

[0177] In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody. In one embodiment, the PD-1 inhibitor is an anti-PD-1 antibody molecule as described in US 2015/0210769, published on Jul. 30, 2015, entitled "Antibody Molecules to PD-1 and Uses Thereof," incorporated by reference in its entirety.

[0178] In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 520. In one embodiment, the anti-PD-1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 506 and a VL comprising the amino acid sequence of SEQ ID NO: 516.

TABLE A

Amino acid and nucleotide sequences of exemplary anti-PD-1 antibody molecules

		BAP049-Clone-B HC
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQAT GQGLEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMEL SSLRSEDTAVYYCTRWTTGTGAYWGQGTTVTVSS
		BAP049-Clone-B LC
SEQ ID NO: 516	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQ KPGKAPKLLIYWASTRESGVPSRFSGSGSGTDFTFTISSLQPEDI ATYYCQNDYSYPYTFGQGTKVEIK

TABLE A-continued

Amino acid and nucleotide sequences of exemplary anti-PD-1 antibody molecules		
BAP049-Clone-E HC		
SEQ ID NO: 506	VH	EVQLVQSGAEVKKPGESLRISCKGSGYTFTTYWMHWVRQAT GQGLEWMGNIYPGTGGSNFDEKFKNRVTITADKSTSTAYMEL SSLRSEDTAVYYCTRWTTGTGAYWGQGTTVTVSS
BAP049-Clone-E LC		
SEQ ID NO: 520	VL	EIVLTQSPATLSLSPGERATLSCKSSQSLLDSGNQKNFLTWYQQ KPGQAPRLLIYWASTRESGVPSRFSGSGSGTDFTFTISSLEAEDA ATYYCQNDYSYPYTFGQGTKVEIK

[0179] In one embodiment, the anti-PD-1 antibody is spartalizumab.

[0180] In one embodiment, the anti-PD-1 antibody is Nivolumab.

[0181] In one embodiment, the anti-PD-1 antibody molecule is Pembrolizumab.

[0182] In one embodiment, the anti-PD-1 antibody molecule is Pidilizumab.

[0183] In one embodiment, the anti-PD-1 antibody molecule is MEDI0680 (Medimmune), also known as AMP-514. MEDI0680 and other anti-PD-1 antibodies are disclosed in U.S. Pat. No. 9,205,148 and WO 2012/145493, incorporated by reference in their entirety. Other exemplary anti-PD-1 molecules include REGN2810 (Regeneron), PF-06801591 (Pfizer), BGB-A317/BGB-108 (Beigene), INCSHR1210 (Incvte) and TSR-042 (Tesaro).

[0184] Further known anti-PD-1 antibodies include those described, e.g., in WO 2015/112800, WO 2016/092419, WO 2015/085847, WO 2014/179664, WO 2014/194302, WO 2014/209804. WO 2015/200119, U.S. Pat. No. 8,735,553, U.S. Pat. No. 7,488,802, U.S. Pat. No. 8,927,697, U.S. Pat. No. 8,993,731, and U.S. Pat. No. 9,102,727, incorporated by reference in their entirety.

[0185] In one embodiment, the anti-PD-1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-1 as, one of the anti-PD-1 antibodies described herein.

[0186] In one embodiment, the PD-1 inhibitor is a peptide that inhibits the PD-1 signaling pathway, e.g., as described in U.S. Pat. No. 8,907,053, incorporated by reference in its entirety. In one embodiment, the PD-1 inhibitor is an immunoadhesin (e.g., an immunoadhesin comprising an extracellular or PD-1 binding portion of PD-L1 or PD-L2 fused to a constant region (e.g., an Fc region of an immunoglobulin sequence). In one embodiment, the PD-1 inhibitor is AMP-224 (B7-DCIg (Amplimmune), e.g., disclosed in WO 2010/027827 and WO 2011/066342, incorporated by reference in their entirety).

PD-L1 Inhibitors

[0187] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with a PD-L 1 inhibitor. In some embodiments, the PD-L 1 inhibitor is chosen from FAZ053 (Novartis), Atezolizumab (Genentech/Roche), Avelumab (Merck Serono and Pfizer), Durvalumab (MedImmune/AstraZeneca), or BMS-936559 (Bristol-Myers Squibb).

[0188] In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule. In one embodiment, the PD-L1 inhibitor is an anti-PD-L1 antibody molecule as disclosed in US 2016/0108123, published on Apr. 21, 2016, entitled "Antibody Molecules to PD-L1 and Uses Thereof," incorporated by reference in its entirety.

[0189] In one embodiment, the anti-PD-L 1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 606 and a VL comprising the amino acid sequence of SEQ ID NO: 616. In one embodiment, the anti-PD-L1 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 620 and a VL comprising the amino acid sequence of SEQ ID NO: 624.

TABLE B

Amino acid and nucleotide sequences of exemplary anti-PD-L1 antibody molecules		
B4P058-Clone O HC		
SEQ ID NO: 606	VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQA RGQRLEWIGRIDPNSGSTKYNEKFKNRFTISRDNSKNTLYLQ MNSLRAEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS
BAP058-Clone O LC		
SEQ ID NO: 616	VL	AIQLTQSPSSLSASVGDRVTITCKASQDVGTAVAWYLQKPGQ SPQLLIYWASTRHTGVPSRFSGSGSGTDFTFTISSLEAEDAATY YCQQYNSYPLTFGQGTKVEIK
BAP058-Cone N HC		
SEQ ID NO: 620	VH	EVQLVQSGAEVKKPGATVKISCKVSGYTFTSYWMYWVRQA TGQGLEWMGRIDPNSGSTKYNEKFKNRVTITADKSTSTAYME LSSLRSEDTAVYYCARDYRKGLYAMDYWGQGTTVTVSS

TABLE B-continued

Amino acid and nucleotide sequences of exemplary anti-PD-L1 antibody molecules		
BAP058-Clone N LC		
SEQ ID NO: 624	VL	DVVMTQSPLSLPVTLGQPASISCKASQDVGTAVAWYQQKPG QAPRLLIYWASTRHTGVPSRFSGSGSGTEFTLTISSLQPDDFAT YYCQQYNSYPLTFGQGTKVEIK

[0190] In one embodiment, the anti-PD-L 1 antibody molecule is Atezolizumab (Genentech/Roche), also known as MPDL3280A, RG7446, RO5541267, YW243.55.S70, or TECENTRIQ®. Atezolizumab and other anti-PD-L1 antibodies are disclosed in U.S. Pat. No. 8,217,149, incorporated by reference in its entirety.

[0191] In one embodiment, the anti-PD-L1 antibody molecule is Avelumab (Merck Serono and Pfizer), also known as MSB0010718C. Avelumab and other anti-PD-L1 antibodies are disclosed in WO 2013/079174, incorporated by reference in its entirety.

[0192] In one embodiment, the anti-PD-L 1 antibody molecule is Durvalumab (MedImmune/AstraZeneca), also known as MEDI4736. Durvalumab and other anti-PD-L1 antibodies are disclosed in U.S. Pat. No. 8,779,108, incorporated by reference in its entirety.

[0193] In one embodiment, the anti-PD-L 1 antibody molecule is BMS-936559 (Bristol-Myers Squibb), also known as MDX-1105 or 12A4. BMS-936559 and other anti-PD-L1 antibodies are disclosed in U.S. Pat. No. 7,943, 743 and WO 2015/081158, incorporated by reference in their entirety.

[0194] Further known anti-PD-L1 antibodies include those described, e.g., in WO 2015/181342, WO 2014/100079, WO 2016/000619, WO 2014/022758. WO 2014/055897, WO 2015/061668, WO 2013/079174, WO 2012/145493, WO 2015/112805, WO 2015/109124, WO 2015/195163, U.S. Pat. No. 8,168,179, U.S. Pat. No. 8,552,154, U.S. Pat. No. 8,460,927, and U.S. Pat. No. 9,175,082, incorporated by reference in their entirety.

[0195] In one embodiment, the anti-PD-L1 antibody is an antibody that competes for binding with, and/or binds to the same epitope on PD-L 1 as, one of the anti-PD-L 1 antibodies described herein.

LAG-3 Inhibitors

[0196] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with a LAG-3 inhibitor. In some embodiments, the LAG-3 inhibitor is chosen from LAG525 (Novartis), BMS-986016 (Bristol-Myers Squibb). TSR-033 (Tesaro), IMP731 or GSK2831781 and IMP761 (Prima BioMed).

[0197] In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule. In one embodiment, the LAG-3 inhibitor is an anti-LAG-3 antibody molecule as disclosed in US 2015/0259420, published on Sep. 17, 2015, entitled "Antibody Molecules to LAG-3 and Uses Thereof," incorporated by reference in its entirety.

[0198] In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 706 and a VL comprising the amino acid sequence of SEQ ID NO: 718. In one embodiment, the anti-LAG-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 724 and a VL comprising the amino acid sequence of SEQ ID NO: 730.

TABLE C

Amino acid and nucleotide sequences of exemplary anti-LAG-3 antibody molecules		
HAP050-Clone I HC		
SEQ ID NO: 706	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAR GQRLEWIGWINTDTGEPTYADDFKGRFVFSLDTSVSTAYLQISS LKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVSS
BAP050-Clone I LC		
SEQ ID NO: 718	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYLQKPGQSP QLLIYYTSTLHLGVPSRFSGSGSGTEFTLTIISSLQPDDFATYYCQ QYYNLPWTFGQGTKVEIK
BAP050-Clone J HC		
SEQ ID NO: 724	VH	QVQLVQSGAEVKKPGASVKVSCKASGFTLTNYGMNWVRQAP GQGLEWMGWINTDTGEPTYADDFKGRFVFSLDTSVSTAYLQI SSLKAEDTAVYYCARNPPYYYGTNNAEAMDYWGQGTTVTVS S
BAP050-Clone J LC		
SEQ ID NO: 730	VL	DIQMTQSPSSLSASVGDRVTITCSSSQDISNYLNWYQQKPGKAP KLLIYYTSTLHLGIPPRFSGSGYGTDFTLTINNIESEDAAYYFCQ QYYNLPWTFGQGTKVEIK

[0199] In one embodiment, the anti-LAG-3 antibody molecule is BMS-986016 (Bristol-Myers Squibb), also known as BMS986016. BMS-986016 and other anti-LAG-3 antibodies are disclosed in WO 2015/116539 and U.S. Pat. No. 9,505,839, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986016, e.g., as disclosed in Table D.

[0200] In one embodiment, the anti-LAG-3 antibody molecule is IMP731 or GSK2831781 (GSK and Prima BioMed). IMP731 and other anti-LAG-3 antibodies are disclosed in WO 2008/132601 and U.S. Pat. No. 9,244,059, incorporated by reference in their entirety. In one embodiment, the anti-LAG-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of IMP731, e.g., as disclosed in Table D.

[0201] Further known anti-LAG-3 antibodies include those described, e.g., in WO 2008/132601, WO 2010/019570, WO 2014/140180, WO 2015/116539, WO 2015/200119, WO 2016/028672, U.S. Pat. No. 9,244,059, U.S. Pat. No. 9,505,839, incorporated by reference in their entirety.

[0202] In one embodiment, the anti-LAG-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on LAG-3 as, one of the anti-LAG-3 antibodies described herein.

[0203] In one embodiment, the anti-LAG-3 inhibitor is a soluble LAG-3 protein, e.g., IMP321 (Prima BioMed), e.g., as disclosed in WO 2009/044273, incorporated by reference in its entirety.

TABLE D

Amino acid sequences of exemplary anti-LAG-3 antibody molecules

		BMS-986016
SEQ ID NO: 762	Heavy chain	QVQLQQWGAGLLKPSETLSLTCAVYGGSFSDYYWNWIRQPPGKG LEWIGEINHRGSTNSNPSLKSRVTLSLDTSKNQFSLKLRSVTAADTA VYYCAFGYSDYEYNWFDPWGQGTLVTVSSASTKGPSVFPLAPCSR STSESTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGL YSLSSVVTVPSSSLGTKTYTCNVDHKPSNTKVDKRVESKYGPPCPP CPAPEFLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSQEDPEVQF NWYVDGVEVHNAKTKPREEQFNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKGLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVS LTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSRL TVDKSRWQEGNVFSCSVMHEALHNHYTQKSLSLSLGK
SEQ ID NO: 763	Light chain	EIVLTQSPATLSLSPGERATLSCRASQSISSYLAWYQQKPGQAPRLL IYDASNRATGIPARFSGSGSGTDFTLTISSLEPEDFAVYYCQQRSNW PLTFGQGTNLEIKRTVAAPSNVFIFPPSDEQLKSGTASVVCLLNNFYP REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADY EKHKVYACEVTHQGLSSPVTKSFNRGEC
		IMP731
SEQ ID NO: 764	Heavy chain	QVQLKESGPGLVAPSQSLSITCTVSGFSLTAYGVNWVRQPPGKGLE WLGMIWDDGSTYNSALKSRLSISKDNSKSQVFLKMNSLQTDDT RYYCAREGDVAFDYWGQGTTLTVSSASTKGPSVFPLAPSSKSTSG GTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSL SSVVTVPSSSLGTQTYICNVNHKPSNTKVDKKVEPKSCDKTHTCPP CPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKF NWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKE YKCKVSNKALPAPIEKTISKAKGQPREPQVYTLPPSRELTKNQVS LTCLVKGFYPSDIAVESESNGQPENNYKTTPPVLDSDSGSFFLYSKL TVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK
SEQ ID NO: 765	Light chain	DIVMTQSPSSLAVSVGQKVTMSCKSSQSLLNGSNQKNYLAWYQQ KPGQSPKLLVYFASTRDSGVPDRFIGSGSGTDFTLTISSVQAEDLAD YFCLQHFGTPPTFGGGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASV VCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSS TLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

TIM-3 Inhibitors

[0204] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with a TIM-3 inhibitor. In some embodiments, the TIM-3 inhibitor is MGB453 (Novartis) or TSR-022 (Tesaro).

[0205] In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule. In one embodiment, the TIM-3 inhibitor is an anti-TIM-3 antibody molecule as disclosed in US 2015/0218274, published on Aug. 6, 2015, entitled "Antibody Molecules to TIM-3 and Uses Thereof," incorporated by reference in its entirety.

[0206] In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 806 and a VL comprising the amino acid sequence of SEQ ID NO: 816. In one embodiment, the anti-TIM-3 antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 822 and a VL comprising the amino acid sequence of SEQ ID NO: 826.

[0207] The antibody molecules described herein can be made by vectors, host cells, and methods described in US 2015/0218274, incorporated by reference in its entirety.

TABLE E

Amino acid and nucleotide sequences of exemplary anti-TIM-3 antibody molecules

		ABTIM3-hum11
SEQ ID NO: 806	VH	QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYNMHWVRQA PGQGLEWMGDIYPGNGDTSYNQKFKGRVTITADKSTSTVY MELSSLRSEDTAVYYCARVGGAFPMDYWGQGTTVTVSS
SEQ ID NO: 816	VL	AIQLTQSPSSLSASVGDRVTITCRASESVEYYGTSLMQWYQQ KPGKAPKLLIYAASNVESGVPSRFSGSGSGTDFTLTISSLQPE DFATYFCQQSRKDPSTFGGGTKVEIK
		ABTIM3-hum03
SEQ ID NO: 822	VH	QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYNMHWVRQ APGQGLEWIGDIYPGQGDTSYNQKFKGRATMTADKSTSTVY MELSSLRSEDTAVYYCARVGGAFPMDYWGGTLVTVSS
SEQ ID NO: 826	VL	DIVLTQSPDSLAVSLGERATINCRASESVEYYGTSLMQWYQ QKPGQPPKLLIYAASNVESGVPDRFSGSGSGTDFTLTISSLQA EDVAVYYCQQSRKDPSTFGGGTKVEIK

[0208] In one embodiment, the anti-TIM-3 antibody molecule is TSR-022 (AnaptysBio/Tesaro). In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of TSR-022. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of APE5137 or APE5121, e.g., as disclosed in Table F. APE5137, APE5121, and other anti-TIM-3 antibodies are disclosed in WO 2016/161270, incorporated by reference in its entirety.

[0209] In one embodiment, the anti-TIM-3 antibody molecule is the antibody clone F38-2E2. In one embodiment, the anti-TIM-3 antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of F38-2E2.

[0210] Further known anti-TIM-3 antibodies include those described, e.g., in WO 2016/111947, WO 2016/071448, WO 2016/144803, U.S. Pat. No. 8,552,156, U.S. Pat. No. 8,841, 418, and U.S. Pat. No. 9,163,087, incorporated by reference in their entirety.

[0211] In one embodiment, the anti-TIM-3 antibody is an antibody that competes for binding with, and/or binds to the same epitope on TIM-3 as, one of the anti-TIM-3 antibodies described herein.

TABLE F

Amino acid sequences of exemplary anti-TIM-3 antibody molecules

		APE5137
SEQ ID NO: 830	VH	EVQLLESGGGLVQPGGSLRLSCAAASGFTFSSYDMSWVRQAPGKGLDW VSTISGGGTYTYYQDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYC ASMDYWGQGTTVTVSSA
SEQ ID NO: 831	VL	DIQMTQSPSSLSASVGDRVTITCRASQSIRRYLNWYHQKPGKAPKLLIYG ASTLQSGVPSRFSGSGSGTDFTLTISSLQPEDFAVYYCQQSHSAPLTFGG GTKVEIKR
		APE5121
SEQ ID NO: 832	VH	EVQVLESGGGLVQPGGSLRLYCVASGFTFSGSYAMSWVRQAPGKGLE WVSAISGSGGSTYYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVY YCAKKYYVGPADYWGQGTLVTVSSG
SEQ ID NO: 833	VL	DIVMTQSPDSLAVSLGERATINCKSSQSVLYSSNNKNYLAWYQHKPGQP PKLLIYWASTRESGVPDRFSGSGSGTDFTLTISSLQAEDVAVYYCQQYYS SPLTFGGGTKIEVK

GITR Agonists

[0212] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with a GITR agonist. In some embodiments, the GITR agonist is GWN323 (NVS), BMS-986156, MK-4166 or MK-1248 (Merck), TRX518 (Leap Therapeutics), INCAGN1876 (Incyte/Agenus), AMG 228 (Amgen) or INBRX-110 (Inhibrx).

[0213] In one embodiment, the GITR agonist is an anti-GITR antibody molecule. In one embodiment, the GITR agonist is an anti-GITR antibody molecule as described in WO 2016/057846, published on Apr. 14, 2016, entitled "Compositions and Methods of Use for Augmented Immune Response and Cancer Therapy," incorporated by reference in its entirety.

[0214] In one embodiment, the anti-GITR antibody molecule comprises a VH comprising the amino acid sequence of SEQ ID NO: 901 and a VL comprising the amino acid sequence of SEQ ID NO: 902.

TABLE G

Amino acid and nucleotide sequences of exemplary anti-GITR antibody molecule

		MAB7
SEQ ID NO: 901	VH	EVQLVESGGGLVQSGGSLRLSCAASGFSLSSYGVDWVRQA PGKGLEWVGVIWGGGGTYYASSLMGRFTISRDNSKNTLYL QMNSLRAEDTAVYYCARHAYGHDGGFAMDYWGQGTLVT VSS
SEQ ID NO: 902	VL	EIVMTQSPATLSVSPGERATLSCRASESVSSNVAWYQQRPG QAPRLLIYGASNRATGIPARFSGSGSGTDFTLTISRLEPEDFA VYYCGQSYSYPFTFGQGTKLEIK

[0215] In one embodiment, the anti-GITR antibody molecule is BMS-986156 (Bristol-Myers Squibb), also known as BMS 986156 or BMS986156. BMS-986156 and other anti-GITR antibodies are disclosed, e.g., in U.S. Pat. No. 9,228,016 and WO 2016/196792, incorporated by reference in their entirety. In one embodiment, the anti-GITR antibody molecule comprises one or more of the CDR sequences (or collectively all of the CDR sequences), the heavy chain or light chain variable region sequence, or the heavy chain or light chain sequence of BMS-986156, e.g., as disclosed in Table H.

[0216] In one embodiment, the anti-GITR antibody molecule is MK-4166 or MK-1248 (Merck). MK-4166, MK-1248, and other anti-GITR antibodies are disclosed, e.g., in U.S. Pat. No. 8,709,424, WO 2011/028683. WO 2015/026684, and Mahne et al. *Cancer Res.* 2017; 77(5): 1108-1118, incorporated by reference in their entirety.

[0217] In one embodiment, the anti-GITR antibody molecule is TRX518 (Leap Therapeutics). TRX518 and other anti-GITR antibodies are disclosed, e.g., in U.S. Pat. No. 7,812,135, U.S. Pat. No. 8,388,967, U.S. Pat. No. 9,028,823, WO 2006/105021, and Ponte J et al. (2010) *Clinical Immunology;* 135:S96, incorporated by reference in their entirety.

[0218] In one embodiment, the anti-GITR antibody molecule is INCAGN1876 (Incyte/Agenus). INCAGN1876 and other anti-GITR antibodies are disclosed, e.g., in US 2015/0368349 and WO 2015/184099, incorporated by reference in their entirety.

[0219] In one embodiment, the anti-GITR antibody molecule is AMG 228 (Amgen). AMG 228 and other anti-GITR antibodies are disclosed, e.g., in U.S. Pat. No. 9,464,139 and WO 2015/031667, incorporated by reference in their entirety.

[0220] In one embodiment, the anti-GITR antibody molecule is INBRX-110 (Inhibrx). INBRX-110 and other anti-GITR antibodies are disclosed, e.g., in US 2017/0022284 and WO 2017/015623, incorporated by reference in their entirety.

[0221] In one embodiment, the GITR agonist (e.g., a fusion protein) is MEDI 1873 (MedImmune), also known as MEDI1873. MEDI 1873 and other GITR agonists are disclosed, e.g., in US 2017/0073386, WO 2017/025610, and Ross et al. *Cancer Res* 2016; 76(14 Suppl): Abstract nr 561, incorporated by reference in their entirety. In one embodiment, the GITR agonist comprises one or more of an IgG Fc domain, a functional multimerization domain, and a receptor binding domain of a glucocorticoid-induced TNF receptor ligand (GITRL) of MEDI 1873.

[0222] Further known GITR agonists (e.g., anti-GITR antibodies) include those described, e.g., in WO 2016/054638, incorporated by reference in its entirety.

TABLE I

Amino acid and nucleotide sequences of exemplary IL-15/IL-15Ra complexes

NIZ985		
SEQ ID NO: 1001	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLLE LQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEEK NIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1002	Human Soluble IL-15Ra	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIRDPALVHQRPAPPSTVTTAGVTPQPESLS PSGKEPAASSPSSNNTAATTAAIVPGSQLMPSKSPSTGTTEISSHESS HGTPSQTTAKNWELTASASHQPPGVYPQG

[0223] In one embodiment, the anti-GITR antibody is an antibody that competes for binding with, and/or binds to the same epitope on GITR as, one of the anti-GITR antibodies described herein.

[0224] In one embodiment, the GITR agonist is a peptide that activates the GITR signaling pathway. In one embodiment, the GITR agonist is an immunoadhesin binding fragment (e.g., an immunoadhesin binding fragment comprising an extracellular or GITR binding portion of GITRL) fused to a constant region (e.g., an Fc region of an immunoglobulin sequence).

TABLE H

Amino acid sequence of exemplary anti-GITR antibody molecules

BMS-986156		
SEQ ID NO: 920	VH	QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGK GLEWVAVIWYEGSNKYYADSVKGRFFISRDNSKNTLYLQMNSL RAEDTAVYYCARGGSMVRGDYYYGMDVWGQGTTVTVSS
SEQ ID NO: 921	VL	AIQLTQSPSSLSASVGDRVTITCRASQGISSALAWYQQKPGKAPK LLIYDASSLESGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQF NSYPYTFGGTKLEIK

IL15/IL-15Ra complexes

[0225] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with an IL-15/IL-15Ra complex. In some embodiments, the IL-15/IL-15Ra complex is chosen from NIZ985 (Novartis), ATL-803 (Altor) or CYP0150 (Cytune).

[0226] In one embodiment, the IL-15/IL-15Ra complex comprises human IL-15 complexed with a soluble form of human IL-15Ra. The complex may comprise IL-15 covalently or noncovalently bound to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 is noncovalently bonded to a soluble form of IL-15Ra. In a particular embodiment, the human IL-15 of the composition comprises an amino acid sequence of SEQ ID NO: 1001 in Table I and the soluble form of human IL-15Ra comprises an amino acid sequence of SEQ ID NO: 1002 in Table I, as described in WO 2014/066527, incorporated by reference in its entirety. The molecules described herein can be made by vectors, host cells, and methods described in WO 2007/084342, incorporated by reference in its entirety.

[0227] In one embodiment, the IL-15/IL-15Ra complex is ALT-803, an IL-15/IL-15Ra Fc fusion protein (IL-15N72D: IL-15RaSu/Fc soluble complex). ALT-803 is disclosed in WO 2008/143794, incorporated by reference in its entirety. In one embodiment, the IL-15/IL-15Ra Fc fusion protein comprises the sequences as disclosed in Table J.

[0228] In one embodiment, the IL-15/IL-15Ra complex comprises IL-15 fused to the sushi domain of IL-15Ra (CYP0150, Cytune). The sushi domain of IL-15Ra refers to a domain beginning at the first cysteine residue after the signal peptide of IL-15Ra, and ending at the fourth cysteine residue after said signal peptide. The complex of IL-15 fused to the sushi domain of IL-15Ra is disclosed in WO 2007/04606 and WO 2012/175222, incorporated by reference in their entirety. In one embodiment, the IL-15/IL-15Ra sushi domain fusion comprises the sequences as disclosed in Table J.

TABLE J

Amino acid sequences of other exemplary IL-15/1L-15Ra complexes

	ALT-803 (Altor)	
SEQ ID NO: 10033	IL-I5N72D	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTA MKCFLLELQVISLESGDASIHDTVENLIILANDSLSSNGN VTESGCKECEELEEKNIKEFLQSFVHIVQMFINTS
SEQ ID NO: 1004	IL-15RaSu/Fc	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIREPKSCDKTHTCPPCPAPELLGGPSVFLFP PKPKDTLMISRTPEVTCVVYDVSHEDPEVKFNWYVDGVEVHNAKT KPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEK TISKAKGQPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEW ESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSV MHEALHNHYTQKSLSLSPGK
	IL-15/IL-5Ra sushi domain fusion (Cytune)	
SEQ ID NO: 1005	Human IL-15	NWVNVISDLKKIEDLIQSMHIDATLYTESDVHPSCKVTAMKCFLL LQVISLESGDASIHDTVENLIILANNSLSSNGNVTESGCKECEELEXK NIKEFLQSFVHIVQMFINTS Where X is E or K
SEQ ID NO: 1006	Human IL-15Ra sushi and hinge domains	ITCPPPMSVEHADIWVKSYSLYSRERYICNSGFKRKAGTSSLTECVL NKATNVAHWTTPSLKCIRDPALVHQRPAPP

CTLA-4 Inhibitors

[0229] In one aspect of the invention, the IL-1β inhibitor or a functional fragment thereof is administered together with an inhibitor of CTLA-4. In some embodiments, the CTLA-4 inhibitor is an anti-CTLA-4 antibody or fragment thereof. Exemplary anti-CTLA-4 antibodies include Tremelimumab (formerly ticilimumab, CP-675.206); and Ipilimumab (MDX-010, Yervoy®).

[0230] In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof for use in the treatment of lung cancer, especially NSCLC, wherein said IL-1β antibody or a functional fragment thereof is administered in combination with one or more chemotherapeutic agent, wherein said one or more chemotherapeutic agent is a check point inhibitor, preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, PDR-001 (spartalizumab) and Ipilimumab. In one embodiment the one or more chemotherapeutic agent is a PD-1 or PD-L-1 inhibitor, preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, PDR-001 (spartalizumab). Typically cancer having at least partial inflammatory basis includes but not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer. In one further embodiment, the IL-1β antibody is canakinumab or a functional fragment thereof. In one further embodiment, the IL-1β antibody is canakinumab or a functional fragment thereof. In one embodiment canakinumab is administered at a dose of 300 mg monthly. In one embodiment canakinumab is administered at a dose of 200 mg every 3 weeks or monthly. In one embodiment canakinumab is administered subcutaneously. In one further embodiment, the IL-1β antibody is canakinumab or a functional fragment thereof is administered in combination with a PD-1 or PD-L1 inhibitor, preferably selected from nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and PDR-001 (spartalizumab), particularly with atezolizumab, wherein canakinumab is administered at the same time of the PD-1 or PD-L 1 inhibitor. In one further embodiment, the IL-1β antibody is gevokizumab or a functional fragment thereof. In one embodiment gevokizumab is administered at a dose of 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg or 60 mg to 90 mg every 3 weeks. In one embodiment gevokizumab or a functional fragment thereof is administered at a dose of 120 mg every 3 weeks. In one embodiment, gevokizumab is administered every month at a dose of 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg or 60 mg to 90 mg. In one embodiment gevokizumab or a functional fragment thereof is administered at a dose of 120 mg every 4 weeks (monthly). In one embodiment gevokizumab is administered subcutaneously or preferably intravenously.

[0231] In one further embodiment, the IL-1β antibody is gevokizumab or a functional fragment thereof is administered in combination with a PD-1 or PD-L1 inhibitor, preferably selected from nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and PDR-001/spartalizumab, particularly with atezolizumab, wherein gevokizumab is administered at the same time as the PD-1 or PD-L1 inhibitor.

[0232] In one embodiment said patient has a tumor that has high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with or without EGFR or ALK genomic tumor aberrations. In one embodiment said patient has tumor that has PD-L 1 expression (TPS≥1%) as determined by an FDA-approved test.

[0233] The term "in combination with" is understood as the two or more drugs are administered subsequently or simultaneously. Alternatively, the term "in combination with" is understood that two or more drugs are administered in the manner that the effective therapeutical concentration of the drugs are expected to be overlapping for a majority of the period of time within the patient's body. The DRUG of

the invention and one or more combination partner (e.g. another drug, also referred to as "therapeutic agent" or "co-agent") may be administered independently at the same time or separately within time intervals, especially where these time intervals allow that the combination partners show a cooperative. e.g. synergistic effect. The terms "co-administration" or "combined administration" or the like as utilized herein are meant to encompass administration of the selected combination partner to a single subject in need thereof (e.g. a patient), and are intended to include treatment regimens in which the agents are not necessarily administered by the same route of administration or at the same time. The drug administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the two compounds in the body of the patient and the treatment regimen will provide beneficial effects of the drug combination in treating the conditions or disorders described herein. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0234] In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof or gevokizumab or a functional fragment thereof, for use in the treatment of lung cancer, wherein the lung cancer is an advanced, metastatic, relapsed, and/or refractory lung cancer. In one embodiment, the lung cancer is metastatic NSCLC.

[0235] In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof or gevokizumab or a functional fragment thereof, for use as the first line treatment of cancer having at least a partial inflammatory basis. Typically cancer having at least partial inflammatory basis includes but is not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer. In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof or gevokizumab or a functional fragment thereof, for use as the first line treatment of cancer having at least a partial inflammatory basis, including lung cancer, especially NSCLC, especially for patients with expression or overexpression of IL-1β or IL-1 receptor. The term "first line treatment" means said patient is given the IL-1β antibody or a functional fragment thereof before the patient develops resistance to one or more other chemotherapeutic agent. Preferably one or more other chemotherapeutic agent is a platinum-based mono or combination therapy, a targeted therapy, such a tyrosine inhibitor therapy, a checkpoint inhibitor therapy or any combination thereof. As first line treatment, the IL-1β antibody or a functional fragment thereof, such as canakinumab or gevokizumab, can be administered to patient as monotherapy or preferably in combination with an check point inhibitor, particularly a PD-1 or PD-L1 inhibitor, particularly atezolizumab, with or without one or more small molecule chemotherapeutic agent.

[0236] In one preferred embodiment, canakinumab or a fragment thereof is used as the first line treatment of lung cancer, especially NSCLC, in combination with one check point inhibitor. As first line treatment, the IL-1β antibody or a functional fragment thereof can be administered to patient as monotherapy or preferably in combination with standard of care, such as one or more chemotherapeutic agent, especially with FDA-approved therapy for lung cancer, especially for NSCLC. In one preferred embodiment, canakinumab or a fragment thereof is used as the first line treatment of lung cancer, especially NSCLC, in combination with one check point inhibitor, preferably with a checkpoint inhibitor selected from nivolumab, pembrolizumab and PDR-001/spartalizumab avelumab, durvalumab and atezolizumab, preferably atezolizumab. In one preferred embodiment, said checkpoint inhibitor is pembrolizumab. In one preferred embodiment, said checkpoint inhibitor is spartalizumab. In one further preferred embodiment, at least one more chemotherapeutic agent is added on top of the combination above, preferably a platinum agent, such as cisplatin or a mitotic inhibitor, such as docetaxel. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously, subsequently or preferably simultaneously with the checkpoint inhibitor.

[0237] In one preferred embodiment, gevokizumab or a fragment thereof is used as the first line treatment of lung cancer, especially NSCLC, in combination with one checkpoint inhibitor, preferably with a PD-1/PD-L1 inhibitor selected from nivolumab, pembrolizumab and PDR-001/spartalizumab, avelumab, durvalumab and atezolizumab, preferably atezolizumab. In one preferred embodiment, said checkpoint inhibitor is pembrolizumab. In one preferred embodiment, said checkpoint inhibitor is spartalizumab. In one further preferred embodiment, at least one more chemotherapeutic agent is added on top of the combination above, preferably a platinum agent, such as cisplatin or a mitotic inhibitor, such as docetaxel. In one embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg every 3 weeks or at a dose of 120 mg every 3 or 4 weeks or at a dose of 90 mg every 3 or 4 weeks, preferably intravenously, subsequently or preferably simultaneously with the checkpoint inhibitor.

[0238] In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably canakinumab or a functional fragment thereof or gevokizumab or a functional fragment thereof, for use as the second or third line treatment of cancer having at least a partial inflammatory basis, including lung cancer, especially NSCLC. The term "the second or third line treatment" means IL-1β antibody or a functional fragment thereof is administered to a patient with cancer progression on or after one or more other chemotherapeutic agent treatment, especially disease progression on or after FDA-approved therapy for lung cancer, especially for NSCLC. Preferably one or more other chemotherapeutic agent is a platinum-based mono or combination therapy, a targeted therapy, such a tyrosine inhibitor therapy, a checkpoint inhibitor therapy or any combination thereof. As the second or third line treatment, the IL-1β antibody or a functional fragment thereof can be administered to the patient as monotherapy or preferably in combination with one or more chemotherapeutic agent, including the continuation of the early treatment with the same one or more chemotherapeutic agent.

[0239] For use as the second or third line treatment, the IL-1β antibody or a functional fragment thereof, such as canakinumab or gevokizumab, can be administered to

patient as monotherapy or preferably in combination with a check-point inhibitor, particularly a PD-1 or PD-L1 inhibitor, particularly atezolizumab, with or without one or more small molecule chemotherapeutic agent.

[0240] In one preferred embodiment, canakinumab or a fragment thereof is used as second or third line treatment of lung cancer, especially NSCLC, in combination with one check point inhibitor, preferably with a checkpoint inhibitor selected from nivolumab, pembrolizumab and PDR-001/spartalizumab (Novartis), ipilimumab and atezolizumab, preferably atezolizumab. In one preferred embodiment, said checkpoint inhibitor is pembrolizumab. In one preferred embodiment, said checkpoint inhibitor is spartalizumab. In one further preferred embodiment, at least one more chemotherapeutic agent is added on top of the combination above, preferably a platinum agent, such as cisplatin or a mitotic inhibitor, such as docetaxel. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously, subsequently or preferably simultaneously with the checkpoint inhibitor.

[0241] In one preferred embodiment, gevokizumab or a fragment thereof is used as second or third line treatment of lung cancer, especially NSCLC or colorectal cancer, in combination with one check-point inhibitor, preferably with a PD-1/PD-L1 inhibitor selected from nivolumab, pembrolizumab and PDR-001/spartalizumab (Novartis) and atezolizumab, preferably atezolizumab. In one further preferred embodiment, at least one more chemotherapeutic agent is added on top of the combination above, preferably a platinum agent, such as cisplatin or a mitotic inhibitor, such as docetaxel. In one embodiment, gevokizumab is administered at a dose of 60 mg to 90 mg every 3 weeks or at a dose of 120 mg every 3 or 4 weeks, preferably intravenously, subsequently or preferably simultaneously with the checkpoint inhibitor.

[0242] In one embodiment, the present invention provides an IL-1β antibody or a functional fragment thereof for use in the treatment of lung cancer in a subject as adjuvant therapy following standard of care for each stage, wherein patient has high risk NSCLC (Stage IB, 2 or 3A), wherein the lung cancer has been surgically removed (surgical resection). In one embodiment, said adjuvant treatment will last for at least 6 months, preferably at least one year, preferably one year. In one embodiment, said IL-1β antibody or a functional fragment thereof is gevokizumab. In one embodiment, said IL-1β antibody or a functional fragment thereof is canakinumab. In one embodiment, canakinumab is administered at a dose of 300 mg monthly, preferably for at least one year. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly, preferably subcutaneously, preferably for at least one year.

[0243] In one embodiment, the present invention provides canakinumab or a functional fragment thereof for use in the treatment of lung cancer in a subject as adjuvant therapy following surgical removal of the lung cancer. Preferably, said patient has completed standard chemotherapy treatment, for example 4 cycles of cisplatin based chemotherapy. In one embodiment, canakinumab is administered monthly at a dose of 200 mg, preferably for at least one year. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly, preferably subcutaneously, preferably for at least one year. In one embodiment the present invention provides an IL-1β antibody or a functional fragment thereof for use as the first line treatment of NSCLC in a patient, wherein said patient has Stage 3B (not amenable to chemo/radiation) or stage 4 disease, alone or preferably in combination with standard of care. In one embodiment, said IL-1β antibody or a functional fragment thereof is gevokizumab. In one embodiment, said IL-1β antibody or a functional fragment thereof is canakinumab. In one embodiment, canakinumab is administered monthly at a dose of at least 300 mg, preferably monthly at a dose of 300 mg. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks or monthly, preferably subcutaneously. In one embodiment the present invention provides an IL-1β antibody or a functional fragment thereof for use in the treatment of NSCLC in patients, wherein said patient has disease progression on or after the treatment with one or more checkpoint inhibitors, preferably a PD-1/PD-L1 inhibitor, preferably atezolizumab. In one embodiment, said patient has disease progression after treatment with one or more chemotherapeutic agent other than one or more checkpoint inhibitors, preferably a PD-1 inhibitor, preferably atezolizumab. In one embodiment said PD-1 inhibitor is selected from nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and PDR-001 (spartalizumab). In one embodiment, said IL-1β antibody or a functional fragment thereof is gevokizumab. In one embodiment, said IL-1β antibody or a functional fragment thereof is canakinumab. In one embodiment, canakinumab is administered monthly at a dose of at least 300 mg, preferably monthly at a dose of 300 mg. In one embodiment, canakinumab is administered at a dose of from 200 mg to 300 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks. The IL-1β antibody or a functional fragment thereof, particularly canakinumab or gevokizumab, is administered as monotherapy or preferably in combination with one or more chemotherapeutic agent, including the continuation of the earlier treatment with the same one or more chemotherapeutic agent.

[0244] In one embodiment the present invention provides an IL-1β antibody or a functional fragment thereof for use in the treatment of colorectal cancer (CRC) or gastric-intestinal cancer in a patient as monotherapy or preferably in combination with standard of care. In one embodiment, said IL-1β antibody or a functional fragment thereof is gevokizumab. In one embodiment gevokizumab is administered at a dose of from 60 mg to 90 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment gevokizumab is administered at a dose of 120 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, said IL-1β antibody or a functional fragment thereof is canakinumab. In one embodiment, canakinumab is administered monthly at a dose of at least 300 mg, preferably monthly at a dose of 300 mg. In one embodiment, canakinumab is administered at a dose of from 200 mg to 300 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered 200 mg every 3 weeks.

[0245] In a preferred embodiment the anti-PD-1 antibody molecule is PDR001/spartalizumab.

[0246] In a preferred embodiment the anti-PD-1 antibody molecule is pembrolizumab.

[0247] In a preferred embodiment the anti-PD-1 antibody molecule is atezolizumab.

[0248] In a preferred embodiment the anti-PD-antibody molecule is nivolumab.

[0249] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of renal cell carcinoma (RCC). The term "renal cell carcinoma (RCC)" as used herein refers to a cancer of the kidney arising from the epithelium of the renal tubules within the renal cortex and includes primary renal cell carcinoma, locally advanced renal cell carcinoma, unresectable renal cell carcinoma, metastatic renal cell carcinoma, refractory renal cell carcinoma, and/or cancer drug resistant renal cell carcinoma.

[0250] All the disclosed uses disclosed throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of renal cell carcinoma. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0251] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of renal cell carcinoma (RCC), wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for renal cell carcinoma (RCC). In one embodiment the one or more chemotherapeutic agent is selected from everolimus (Afinitor®), aldesleukin (Proleukin®), bevacizumab (Avastin®), axitinib (Inlyta®), cabozantinib (Cabometyx®), lenvatinib mesylate (Lenvima®), sorafenib tosylate (Nexavar®), nivolumab (Opdivo®), pazopanib hydrochloride (Votrient®), sunitinib malate (Sutent®), temsirolimus (Torisel®), ipilimumab and tivozanib (FOTIVDA®). Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0252] In one embodiment the one or more chemotherapeutic agent is a CTLA-4 checkpoint inhibitor, wherein preferably said CTLA-4 checkpoint inhibitor is ipilimumab. In one embodiment the one or more chemotherapeutic agent is everolimus.

[0253] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L1 inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0254] In one embodiment the one or more chemotherapeutic agent is nivolumab. In one embodiment the one or more chemotherapeutic agent are nivolumab plus ipilimumab.

[0255] In one embodiment the or more chemotherapeutic agent is cabozantinib.

[0256] In one embodiment the or more chemotherapeutic agent is Atezolizumab plus bevacizumab.

[0257] In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of renal cell carcinoma (RCC) in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in first line treatment of renal cell carcinoma (RCC). In one embodiment gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of renal cell carcinoma (RCC).

[0258] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0259] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of colorectal cancer (CRC). The term "Colorectal cancer (CRC)", also known as bowel cancer and colon cancer, as used herein means a neoplasm arising from the colon and/or rectum, particularly from the epithelium of the colon and/or rectum and includes colon adenocarcinoma, rectal adenocarcinoma, metastatic colorectal cancer (mCRC), advanced colorectal cancer, refractory colorectal cancer, refractory metastatic microsatellite stable (MSS) colorectal cancer unresectable colorectal cancer, and/or cancer drug resistant colorectal cancer. Up to 25% of patients are diagnosed with metastatic disease at presentation and 50% of patients may go on to develop metastases at some point in life.

[0260] All the disclosed uses disclosed throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of CRC. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0261] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of colorectal cancer (CRC), wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for CRC. In one embodiment the one or more chemotherapeutic agent is selected from irinotecan hydrochloride (Camptosar®), capecitabine (Xeloda®), oxaliplatin (Eloxatin®), 5-FU (fluorouracil), leucovorin calcium (folinic acid), FU-LV/FL (5-FU plus leucovorin), trifluridine/tipiracil hydrochloride (Lonsurf®), nivolumab (Opdivo®), regorafenib (Stivarga®), FOLFOXIRI (leucovorin, 5-fluorouracil [5-FU], oxaliplatin, irinotecan), FOLFOX (leucovorin, 5-FU, oxaliplatin), FOLFIRI (leucovorin, 5-FU, iri-

notecan). CapeOx (capecitabine plus oxaliplatin), XELIRI (capecitabine (Xeloda®) plus irinotecan hydrochloride), XELOX (capecitabine (Xeloda®) plus oxaliplatin), FOLFOX plus bevacizumab (Avastin®), cetuximab (Erbitux®), panitumumab (Vectibix®), FOLFIRI plus Ramucirumab (Cyramza®), FOLFIRI plus cetuximab (Erbitux®), and FOLFIRI plus Ziv-aflibercept (Zaltrap). Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0262] In one embodiment the one or more chemotherapeutic agent is a general cytotoxic agent, wherein preferably said general cytotoxic agent is selected from the list consisting of FOLFOX. FOLFIRI, capecitabine, 5-fluorouracil, irinotecan and oxaliplatin.

[0263] Usually, the initial therapy of CRC involves a cytotoxic backbone of a doublet chemotherapy regimen, combining fluorouracil and oxaliplatin (FOLFOX), fluorouracil and irinotecan (FOLFIRI), or capecitabine and oxaliplatin (XELOX). Bevacizumab is typically recommended upfront combined with chemotherapy. For patients with wild-type RAS tumors anti-EGFR agents (cetuximab and/orpanitumumab) represent alternative options for initial biologic therapy in combination with backbone chemotherapy.

[0264] The term "FOLFOX" as used herein refers to a combination therapy (e.g., chemotherapy) comprising at least one oxaliplatin compound chosen from oxaliplatin, pharmaceutically acceptable salts thereof, and solvates of any of the foregoing; at least one 5-fluorouracil (also known as 5-FU) compound chosen from 5-fluorouracil, pharmaceutically acceptable salts thereof, and solvates of any of the foregoing; and at least one folinic acid compound chosen from folinic acid (also known as leucovorin), levofolinate (the levo isoform of folinic acid), pharmaceutically acceptable salts of any of the foregoing, and solvates of any of the foregoing. The term "FOLFOX" as used herein is not intended to be limited to any particular amounts of or dosing regimens for those components.

[0265] The term "FOLFIRI" as used herein refers to a combination therapy (e.g., chemotherapy) comprising at least one irinotecan compound chosen from irinotecan, pharmaceutically acceptable salts thereof, and solvates of any of the foregoing; at least one 5-fluorouracil (also known as 5-FU) compound chosen from 5-fluorouracil, pharmaceutically acceptable salts thereof, and solvates of any of the foregoing; and at least one compound chosen from folinic acid (also known as leucovorin), levofolinate (the levo isoform of folinic acid), pharmaceutically acceptable salts of any of the foregoing, and solvates of any of the foregoing. The term "FOLFIRI" as used herein is not intended to be limited to any particular amounts of or dosing regimens for these components. Rather, as used herein, "FOLFIRI" includes all combinations of these components in any amounts and dosing regimens.

[0266] In one embodiment the one or more chemotherapeutic agent is a VEGF inhibitor (e.g., an inhibitor of one or more of VEGFR (e.g., VEGFR-1, VEGFR-2, or VEGFR-3) or VEGF).

[0267] Exemplary VEGFR pathway inhibitors that can be used in combination with an IL-3 binding antibody or a functional fragment thereof, suitably gevokizumab, for use in the treatment of cancer with partial inflammatory basis, include, e.g., bevacizumab (also known as rhuMAb VEGF or AVASTIN®), ramucirumab (Cyramza®), ziv-aflibercept (Zaltrap®), cediranib (RECENTIN™, AZD2171), lenvatinib (Lenvima®), vatalanib succinate, axitinib (INLYTA®); brivanib alaninate (BMS-582664, (S)—((R)-1-(4-(4-Fluoro-2-methyl-1H-indol-5-yloxy)-5-methylpyrrolo[2,1-f][1,2,4]triazin-6-yloxy)propan-2-yl)2-aminopropanoate); sorafenib (NEXAVAR®); pazopanib (VOTRIENT®); sunitinib malate (SUTENT®); cediranib (AZD2171, CAS 288383-20-1); vargatef (BIBF1120, CAS 928326-83-4); Foretinib (GSK1363089); telatinib (BAY57-9352, CAS 332012-40-5); apatinib (YN968D1, CAS 811803-05-1); imatinib (GLEEVEC®); ponatinib (AP24534, CAS 943319-70-8); tivozanib (AV951, CAS 475108-18-0); regorafenib (BAY73-4506, CAS 755037-03-7); brivanib (BMS-540215, CAS 649735-46-6); vandetanib (CAPRELSA® or AZD6474); motesanib diphosphate (AMG706, CAS 857876-30-3, N-(2,3-dihydro-3,3-dimethyl-1H-indol-6-yl)-2-[(4-pyridinylmethyl)amino]-3-pyridinecarboxamide described in PCT Publication No. WO 02/066470); semaxanib (SU5416), linfanib (ABT869, CAS 796967-16-3); cabozantinib (XL184, CAS 849217-68-1); lestaurtinib (CAS 111358-88-4); N-[5-[[[5-(1,1-dimethylethyl)-2-oxazolyl]methyl]thio]-2-thiazolyl]-4-piperidinecarboxamide (BMS38703, CAS 345627-80-7); (3R,4R)-4-amino-1-((4-((3-methoxyphenyl)amino)pyrrolo[2,1-f][1,2,4]triazin-5-yl)methyl)piperidin-3-ol (BMS690514); N-(3,4-Dichloro-2-fluorophenyl)-6-methoxy-7-[[(3aα,5β,6aα)-octahydro-2-methylcyclopenta[c]pyrrol-5-yl]methoxy]-4-quinazolinamine (XL647, CAS 781613-23-8); 4-methyl-3-[[1-methyl-6-(3-pyridinyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino]-N-[3-(trifluoromethyl)phenyl]-benzamide (BHG712, CAS 940310-85-0); and endostatin (ENDOSTAR®).

[0268] In one embodiment the one or more chemotherapeutic agent is anti-VEGF antibody. In one embodiment the one or more chemotherapeutic agent is anti-VEGF inhibitor of small molecule weight.

[0269] In one embodiment the one or more chemotherapeutic agent is a VEGF inhibitor is selected from the list consisting of bevacizumab, ramucirumab and ziv-aflibercept. In one preferred embodiment the VEGF inhibitor is bevacizumab.

[0270] In one embodiment the one or more chemotherapeutic agent is FOLFIRI plus bevacizumab or FOLFOX plus bevacizumab.

[0271] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, preferably a PD-1 or PD-L1 inhibitor, preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001). In one preferred embodiment the one or more chemotherapeutic agent is pembrolizumab. In one preferred embodiment the one or more chemotherapeutic agent is nivolumab.

[0272] In one preferred embodiment the one or more chemotherapeutic agent is atezolizumab. In one further preferred embodiment the one or more chemotherapeutic agent is atezolizumab and cobimetinib.

[0273] In one preferred embodiment the one or more chemotherapeutic agent is ramucirumab. In one preferred embodiment said patient has metastatic CRC.

[0274] In one preferred embodiment the one or more chemotherapeutic agent is ziv-aflibercept. In one preferred embodiment said patient has metastatic CRC.

[0275] In one preferred embodiment the one or more chemotherapeutic agent is a a tyrosine kinase inhibitor. In

one embodiment said tyrosine kinase inhibitor is an EGF pathway inhibitor, preferably an inhibitor of Epidermal Growth Factor Receptor (EGFR). Preferably the EGFR inhibitor is chosen from one of more of erlotinib (Tarceva®), gefitinib (Iressa®), cetuximab (Erbitux®), panitumumab (Vectibix®), necitumumab (Portrazza®), dacomitinib, nimotuzumab, imgatuzumab, osimertinib (Tagrisso®), lapatinib (TYKERB®, TYVERB®). In one embodiment said EGFR inhibitor is cetuximab. n one embodiment said EGFR inhibitor is panitumumab.

[0276] In one embodiment, the EGFR inhibitor is (R,E)-N-(7-chloro-1-(1-(4-(dimethylamino)but-2-enoyl)azepan-3-yl)-1H-benzo[d]imidazol-2-yl)-2-methylisonicotinamide (Compound A40) or a compound disclosed in PCT Publication No. WO 2013/184757.

[0277] In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of CRC in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in first line treatment of CRC. In one embodiment gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of CRC.

[0278] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0279] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of gastric cancer.

[0280] As used herein, the term "gastric cancer" encompasses gastric and intestinal cancer and cancer of the esophagus (gastroesophageal cancer), particularly the lower part of the esophagus and refers to primary gastric cancer, metastatic gastric cancer, refractory gastric cancer, unresectable gastric cancer, and/or cancer drug resistant gastric cancer. The term "gastric cancer" includes adenocarcinoma of the distal esophagus, gastroesophageal junction and/or stomach, gastrointestinal carcinoid tumor, and gastrointestinal stromal tumor. In a preferred embodiment, the gastric cancer is gastroesophageal cancer.

[0281] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of gastric cancer. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0282] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of gastric cancer, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for gastric cancer. In one embodiment the one or more chemotherapeutic agent is selected from carboplatin plus paclitaxel (Taxol®), cisplatin plus 5-fluorouracil (5-FU), ECF (epirubicin (Ellence®), cisplatin, and 5-FU), DCF (docetaxel (Taxotere®), cisplatin, and 5-FU), cisplatin plus capecitabine (Xeloda®), oxaliplatin plus 5-FU, oxaliplatin plus capecitabine, irinotecan (Camptosar®) ramucirumab (Cyramzat®), docetaxel (Taxotere®), trastuzumab (Herceptin®), FU-LV/FL (5-fluorouracil plus leucovorin), and XELIRI (capecitabine (Xeloda®) plus irinotecan hydrochloride). Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0283] In one embodiment the one or ore chemotherapeutic agent is paclitaxel and ramucirumab. In one further embodiment said combination is used for second line treatment of metastatic gastroesophageal cancer.

[0284] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0285] In one embodiment the one or more chemotherapeutic agent is nivolumab. In one embodiment the one or more chemotherapeutic agent is nivolumab plus and ipilimumab. In one further embodiment said combination is used for first or second line treatment of metastatic gastroesophageal cancer.

[0286] In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of gastric cancer in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in first line treatment of gastric cancer. In one embodiment gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of gastric cancer.

[0287] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0288] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of melanoma. The term "melanoma" includes "malignant melanoma" and "cutaneous melanoma" and as used herein refers to a malignant tumor arising from melanocyte which are derived from the neural crest. Although most melanomas arise in the skin, they may also arise from mucosal surfaces or at other sites to which neural crest cells migrate. As used herein, the term "melanoma" includes primary melanoma, locally advanced melanoma, unresectable melanoma. BRAF V600 mutated melanoma. NRAS-mutant melanoma, metastatic melanoma (including unresectable or metastatic BRAF V600 mutated melanoma), refractory melanoma (including relapsed or refractory BRAF V600-mutant melanoma (e.g. said melanoma being relapsed after failure of BRAFi/MEKi combination therapy or refractory to BRAFi/MEKi combination therapy), cancer drug resistant melanoma (including BRAF-mutant mela-

noma resistant to BRAFi/MEKi combination treatment) and/or immuno-oncology (IO) refractory melanoma.

[0289] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of melanoma In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly, preferably subcutaneously. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly, preferably intravenously. In one embodiment, gevokizumab is administered at a dose of 90 mg every 3 weeks or monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly.

[0290] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of melanoma, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for melanoma. In one embodiment the one or more chemotherapeutic agent is selected from temozolomide, nab-paclitaxel, paclitaxel, cisplatin, carboplatin, vinblastine, aldesleukin (Proleukin®), cobimetinib (Cotellic®), Dacarbazine, Talimogene Laherparepvec (Imlygic®), (peg)interferon alfa-2b (Intron A®/Sylatron™), Trametinib (Mekinist®), Dabrafenib (Tafinlar®), Trametinib (Mekinist®) plus Dabrafenib (Tafinlar®), pembrolizumab (Kevtruda®), Nivolumab (Opdivo®), Ipilimumab (Yervoy®), Nivolumab (Opdivo®) plus Ipilimumab (Yervoy®), and Vemurafenib (Zelboraf®). Other medicaments currently being development for the treatment of melanoma include atezolizumab (Tecentriq®) and atezolizumab (Tecentriq®) plus bevacizumab (Avastin®). Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0291] Immunotherapies currently in development have started to offer significant benefit to melanoma cancer patients, including those for whom conventional treatments are ineffective. Recently, pembrolizumab (Keytruda®) and nivolumab (Opdivo®), two inhibitors of the PD-1/PD-L1 interaction have been approved for use in melanoma. However, results indicate that many patients treated with single agent PD-1 inhibitors do not benefit adequately from treatment.

[0292] In one embodiment the one or more chemotherapeutic agent is nivolumab.

[0293] In one embodiment the one or more chemotherapeutic agent ipilimumab.

[0294] In one embodiment the one or more chemotherapeutic agent is nivolumab and ipilimumab.

[0295] In one embodiment the one or more chemotherapeutic agent is trametinib.

[0296] In one embodiment the one or more chemotherapeutic agent is Dabrafenib.

[0297] In one embodiment the one or more chemotherapeutic agent is trametinib and dabrafenib.

[0298] In one embodiment the one or more chemotherapeutic agent is Pembrolizumab.

[0299] In one embodiment the one or more chemotherapeutic agent is Atezolizumab.

[0300] In one embodiment the one or more chemotherapeutic agent is atezolizumab (Tecentriq®) plus bevacizumab.

[0301] In one embodiment, gevokizumab or a functional fragment thereof, alone or preferably in combination, is used in the prevention of recurrence or relapse of melanoma in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or in preferably combination, in first line treatment of melanoma. In one embodiment gevokizumab or a functional fragment thereof is used, alone or in preferably combination, in second or third line of melanoma.

[0302] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0303] Like what has been observed concerning IL-1β in the development of lung cancer, it is plausible that IL-1β plays a similar role in the development of melanoma.

[0304] Tumor cells expressing the IL-1β precursor must first activate caspase-1 in order to process the inactive precursor into active cytokine. Activation of caspase-1 requires autocatalysis of procaspase-1 by the nucleotide-binding domain and leucine-rich repeat containing protein 3 (NLRP3) inflammasome (Dinarello, C. A. (2009). Ann Rev Immunol, 27, 519-550). In late-stage human melanoma cells, spontaneous secretion active IL-1 is observed via constitutive activation of the NLRP3 inflammasome (Okamoto, M. et al The Journal of Biological Chemistry, 285, 6477-6488). Unlike human blood monocytes, these melanoma cells require no exogenous stimulation. In contrast, NLRP3 functionality in intermediate stage melanoma cells requires activation of the IL-1 receptor by IL-1α in order to secrete active IL-1β. The spontaneous secretion of IL-1β from melanoma cells was reduced by inhibition of caspase-1 or the use of small interfering RNA directed against the inflammasome component ASC. Supernatants from melanoma cell cultures enhanced macrophage chemotaxis and promoted in vitro angiogenesis, both prevented by pretreating melanoma cells with inhibitors of caspases-1 or IL-1 receptor blockade (Okamoto, M. et al The Journal of Biological Chemistry, 285, 6477-6488). Furthermore, in a screen of human melanoma tumor samples, copy number greater than 1,000 for IL-1β was present in 14 of 16 biopsies, whereas none expressed IL-1α (Elaraj, D. M. et al, Clinical Cancer Research, 12, 1088-1096. Taken together these findings implicate IL-1-mediated autoinflammation, especially IL-1β, as contributing to the development and progression of human melanoma.

[0305] Thus in one aspect, the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in the treatment and/or prevention of melanoma in a patient. In one embodiment, the patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than 2 mg/L or equal to or greater than 4 mg/L.

[0306] In one embodiment, about 90 mg to about 450 mg of an IL-1 binding antibody or a functional fragment thereof in administered to melanoma patient per treatment, preferably every two, three or four weeks (monthly).

[0307] In one embodiment, the IL-1 binding antibody is canakinumab. Preferably 300 mg of canakinumab is administered monthly. Furthermore the second administration of canakinumab is at most two weeks, preferably two weeks

apart from the first administration, furthermore canakinumab is administered subcutaneously. Furthermore canakinumab is administered in a liquid form contained in a prefilled syringe or as a lyophilized form for reconstitution.

[0308] In one embodiment the IL-1β binding antibody is gevokizumab (XOMA-052). Furthermore gevokizumab is administered subcutaneously or intravenously.

[0309] It is the data arisen from CANTOS that provided clinical evidence for the first time of the effectiveness of an IL-1β in the treatment of lung cancer, a cancer that has at least a partial inflammatory basis. Furthermore lung cancer has concomitant inflammation activated or mediated in part through activation of the Nod-like receptor protein 3 (NLRP3) inflammasome with consequent local production of interleukin-1β. It is plausible that melanoma shares similar mechanism in terms of the involvement of IL-1β in cancer development. Thus it is plausible that an IL-1β binding antibody or a functional fragment thereof, especially canakinumab, is effective in the treatment of melanoma.

[0310] All the teachings disclosed in the present application concerning the use of an IL-1β binding antibody or a functional fragment thereof, especially canakinumab or gevokizumab, particularly regarding the dosing regimen of canakinumab or gevokizumab, particularly regarding the patients' hsCRP level and its reduction by the treatment, particularly regarding the use of hsCRP as biomarker, in the treatment and/or prevention of lung cancer are equally applicable or can be easily modified by a skilled person, in the treatment and/or prevention of melanoma.

[0311] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of bladder cancer. The term "bladder cancer" as used herein refers to squamous cell carcinoma of the bladder, adenocarcinoma of the bladder, small cell carcinoma of the bladder and urothelial (cell) carcinoma, i.e. carcinomas of the urinary bladder, ureter, renal pelvis and urethra. The term includes reference to the non muscle-invasive (NMI) or superficial forms, as well as to the muscle invasive (MI) types. Also included in the term is reference to primary bladder cancer, locally advanced bladder cancer, unresectable bladder cancer, metastatic bladder cancer, refractory bladder cancer, relapsed bladder cancer and/or cancer drug resistant bladder cancer. All the disclosed uses throughout this application, including but not being limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of bladder cancer. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0312] Treatment regimens of bladder cancer include intravesical therapy for early stages of bladder cancer as well as chemotherapy with and without radiation therapy.

[0313] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of bladder cancer, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for bladder cancer. In one embodiment the one or more chemotherapeutic agent is selected from cisplatin, cisplatin plus fluorouracil (5-FU), mitomycin plus 5-FU, gemcitabine plus cisplatin, MVAC (methotrexate, vinblastine, doxorubicin (adriamycin), plus cisplatin), CMV (cisplatin, methotrexate, and vinblastine), carboplatin plus paclitaxel or docetaxel, gemcitabine, cisplatin, carboplatin, docetaxel, paclitaxel, doxorubicin, 5-FU, methotrexate, vinblastine, ifosfamide, pemetrexed, thiotepa, valrubicin, atezolizumab (Tecentriq®), avelumab (Bavencio®), durvalumab (Imfinzi®), pembrolizumab (Keytruda®) and nivolumab (Opdivo®).

[0314] Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0315] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L1 inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0316] In one embodiment, gevokizumab or a functional fragment thereof is used in the prevention of recurrence or relapse of bladder cancer in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used in first line treatment of bladder cancer. In one embodiment gevokizumab or a functional fragment thereof is used in second or third line of bladder cancer.

[0317] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0318] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of prostate cancer. The term "prostate cancer" as used herein, refers to acinar adenocarcinoma, ductal adenocarcinoma, squamous cell prostate cancer, small cell prostate cancer and includes androgen-deprivation/castration-sensitive prostate cancer, androgen-deprivation/castration-resistant prostate cancer, primary prostate cancer, locally advanced prostate cancer, unresectable prostate cancer, metastatic prostate cancer, refractory prostate cancer, relapsed prostate cancer and/or cancer drug resistant prostate cancer.

[0319] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of prostate cancer. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably

monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0320] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of prostate cancer, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for prostate cancer. In one embodiment the one or more chemotherapeutic agent is selected from abiraterone, apalutamide, bicalutamide, cabazitaxel, degarelix, docetaxel, docetaxel plus prednisone, enzalutamide (Xtandi®), flutamide, goserelin acetate, leuprolide acetate, ketoconazole, aminoglutethamide, mitoxantrone hydrochloride, nilutamide, sipuleucel-T, radium 223 dichloride, estramustine, rilimogene galvacirepvec/rilimogene glafolivec (PROSTVAC®), pembrolizumab (Keytruda®), pembrolizumab plus enzalutamide.

[0321] Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0322] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L1 inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0323] In one embodiment, gevokizumab or a functional fragment thereof is used in the prevention of recurrence or relapse of prostate cancer in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used in first line treatment of prostate cancer. In one embodiment gevokizumab or a functional fragment thereof is used in second or third line of prostate cancer.

The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0324] In certain embodiments, the present invention provides an IL-1β antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of breast cancer. The term "breast cancer" as used herein includes breast cancer arising in ducts (ductal carcinoma, including invasive ductal carcinoma and ductal carcinoma in situ (DCIS)), glands (lobular carcinoma, including Invasive lobular carcinoma, and lobular carcinoma in situ (LCIS), inflammatory breast cancer, angiosarcoma, and including but not limited to, estrogen-receptor-positive (ER+) breast cancer, progesterone-receptor-positive (PR+) breast cancer, herceptin-receptor positive (HER2+) breast cancer, herceptin-receptor negative (HER2−) breast cancer. ER-positive/HER2-negative breast cancer and triple negative breast cancer (TNBC; a breast cancer that is HER2−, ER− and PR−).

[0325] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of breast cancer. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0326] Treatment regimens of breast cancer include intravesical therapy for early stages of breast cancer as well as chemotherapy with and without radiation therapy.

[0327] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of breast cancer, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for breast cancer. In one embodiment the one or more chemotherapeutic agent is selected from abemaciclib, methotrexate, abraxane (paclitaxel albumin-stabilized nanoparticle formulation), ado-trastuzumab emtansine, anastrozole, pamidronate disodiumrozole, capecitabine, cyclophosphamide, docetaxel, doxorubicin hydrochloride, epirubicin hydrochloride, eribulin mesylate, exemestane, fluorouracil injection, fulvestrant, gemcitabine hydrochloride, goserelin acetate, ixabepilone, lapatinib ditosylate, letrozole, megestrol acetate, methotrexate, neratinib maleate, olaparib, paclitaxel, pamidronate disodium, tamoxifen, thiotepa, toremifene, vinblastine sulfate, AC (doxorubicin hydrochloride (adriamycin) and cyclophosphamide), AC-T (doxorubicin hydrochloride (adriamycin), cyclophosphamide and paclitaxel), CAF (cyclophosphamide, doxorubicin hydrochloride (adriamycin) and fluorouracil), CMF (cyclophosphamide, methotrexate and fluorouracil), FEC (fluorouracil, epirubicin hydrochloride, cyclophosphamide), TAC (docetaxel (taxotere), doxorubicin hydrochloride (adriamycin), cyclophosphamide), palbociclib, abemaciclib, ribociclib, everolimus, trastuzumab (Herceptin®), ado-trastuzumab emtansine (Kadcyla®), vorinostat (Zolinza®), romidepsin (Istodax®), chidamide (Epidaza®), panobinostat (Farydak®), belinostat (Beleodaq®, pxd101), valproic acid (Depakote®, Depakene®, Stavzor®), mocetinostat (mgcd0103), abexinostat (pci-24781), entinostat (ms-275), pracinostat (sb939), resminostat (4sc-201), givinostat (itf2357), quisinostat (jnj-26481585), kevetnn, cudc-101, ar-42, tefinostat (chr-2835), chr-3996, 4sc202, cg200745, rocilinostat (acy-1215), sulforaphane, or a checkpoint inhibitor such as nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab spartalizumab (PDR-001), and ipilimumab.

[0328] Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0329] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0330] In one preferred embodiment IL-1β antibody or a functional fragment thereof, preferably canakinumab or gevokizumab, is used in combination of one or more chemotherapeutic agents, wherein said agent is an anti-Wnt

inhibitor, preferably Vantictumab. This embodiment is particularly useful in the inhibition of breast tumor metastasis.

[0331] In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of breast cancer in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is use, alone or preferably in combination, in first line treatment of breast cancer. In one embodiment gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of breast cancer. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the treatment of TNBC.

[0332] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0333] In certain embodiments, the present invention provides an IL-1 antibody or a functional fragment thereof, suitably gevokizumab or a functional fragment thereof, suitably canakinumab or a functional fragment thereof, for use in the treatment of pancreatic cancer.

[0334] As used herein, the term "pancreatic cancer" refers to pancreatic endocrine and pancreatic exocrine tumors and includes adenocarcinoma arising from pancreatic ductal epithelium, suitably pancreatic ductal adenocarcinoma (PDAC) or a neoplasm arising from pancreatic islet cells and includes pancreatic neuroendocrine tumors (pNETs) such as gastrinoma, insulinoma, glucagonoma, VIPomas and somatostatinomas. The pancreatic cancer may be primary pancreatic cancer, locally advanced pancreatic cancer, unresectable pancreatic cancer, metastatic pancreatic cancer, refractory pancreatic cancer, and/or cancer drug resistant pancreatic cancer.

[0335] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the treatment of pancreatic cancer. In one embodiment, canakinumab is administered at a dose of from 200 mg to 400 mg per treatment, wherein canakinumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, canakinumab is administered at a dose of 200 mg every 3 weeks, preferably subcutaneously. In one embodiment, gevokizumab is administered at a dose of from 90 mg to 200 mg per treatment, wherein gevokizumab is administered preferably every 3 weeks or preferably monthly. In one embodiment, gevokizumab is administered at a dose of 120 mg every 3 weeks or monthly, preferably intravenously.

[0336] In one embodiment, the present invention provides gevokizumab or a functional fragment thereof, for use in the treatment of pancreatic cancer, wherein gevokizumab, or a functional fragment thereof, is administered in combination with one or more chemotherapeutic agent. In one embodiment the chemotherapeutic agent is the standard of care agent for gastric cancer. In one embodiment the one or more chemotherapeutic agent is selected from nab-paclitaxel (Paclitaxel Albumin-stabilized Nanoparticle Formulation; Abraxane®), docetaxel, capecitabine, everolimus (Afinitor®), erlotinib hydrochloride (Tarceva®), sunitinib malate (Sutent®), fluorouracil (5-FU), gemcitabine hydrochloride, irinotecan, mitomycin C, FOLFIRINOX (leucovorin calcium (folinic acid), fluorouracil, irinotecan hydrochloride and oxaliplatin), gemcitabine plus cisplatin, gemcitabine plus oxaliplatin, gemcitabine plus nab-paclitaxel, and OFF (oxaliplatin, fluorouracil and leucovorin calcium (folinic acid)). Depending on the patient condition, at least one, at least two or at least three chemotherapeutic agents can be selected from the list above, to be combined with gevokizumab.

[0337] In one embodiment the one or more chemotherapeutic agent is a checkpoint inhibitor, wherein preferably is a PD-1 or PD-L1 inhibitor, wherein preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0338] In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of pancreatic cancer in a patient after said cancer has been surgically removed. In one embodiment, gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in first line treatment of pancreatic cancer. In one embodiment gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of pancreatic cancer.

[0339] The above disclosed embodiments for gevokizumab or a functional fragment thereof are suitably applicable for canakinumab or a functional fragment thereof.

[0340] In one aspect, the present invention provides a pharmaceutical composition comprising an IL-1β binding antibody or a functional fragment thereof and at least one pharmaceutically acceptable carrier for use in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer in a patient. Preferably the pharmaceutical composition comprises a therapeutically effective amount of IL-1β binding antibody or a functional fragment thereof.

[0341] In one aspect of this invention canakinumab or a functional fragment thereof is administered intravenously. In one aspect of this invention canakinumab or a functional fragment thereof is preferably administered subcutaneously.

[0342] In one aspect of this invention gevokizumab or a functional fragment thereof is administered subcutaneously. In one aspect of this invention gevokizumab or a functional fragment thereof is preferably administered intravenously.

[0343] Canakinumab can be administered in a reconstituted formulation comprising comprising canakinumab at a concentration of 50-200 mg/ml, 50-300 mM sucrose, 10-50 mM histidine, and 0.01-0.1% surfactant and wherein the pH of the formulation is 5.5-7.0. Canakinumab can be administered in a reconstituted formulation comprising canakinumab at a concentration of 50-200 mg/ml, 270 mM sucrose, 30 mM histidine and 0.06% polysorbate 20 or 80, wherein the pH of the formulation is 6.5.

[0344] Canakinumab can also be administered in a liquid formulation comprising canakinumab at a concentration of 50-200 mg/ml, a buffer system selected from the group consisting of citrate, histidine and sodium succinate, a stabilizer selected from the group consisting of sucrose, mannitol, sorbitol, arginine hydrochloride, and a surfactant and wherein the pH of the formulation is 5.5-7.0. Canakinumab can also be administered in a liquid formulation comprising canakinumab at a concentration of 50-200 mg/ml, 50-300 mM mannitol, 10-50 mM histidine and 0.01-0.1% surfactant, and wherein the pH of the formulation is 5.5-7.0. Canakinumab can also be administered in a liquid formulation comprising canakinumab at a concentration of

50-200 mg/ml, 270 mM mannitol, 20 mM histidine and 0.04% polysorbate 20 or 80, wherein the pH of the formulation is 6.5.

[0345] When administered subcutaneously, canakinumab can be administered to the patient in a liquid form contained in a prefilled syringe or as a lyophilized form for reconstitution.

[0346] In one aspect, the present invention provides high sensitivity C-reactive protein (hsCRP) for use as a biomarker in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, with an IL-1β inhibitor, IL-1β binding antibody or a functional fragment thereof. Typically cancers that have at least a partial inflammatory basis include but are not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer. AML, multiple myeloma and pancreatic cancer. Consistent with prior work indicating a strong inflammatory component to certain cancers, hsCRP levels in the CANTOS trial population were elevated at baseline among those who were diagnosed with lung cancer during follow-up compared to those who remained free of any cancer diagnosis (6.0 versus 4.2 mg/L, P<0.001). Thus the level of hsCRP is possibly relevant in determining whether a patient with diagnosed lung cancer, undiagnosed lung cancer or is at risk of developing lung cancer should be treated with an IL-1β inhibitor, IL-1β binding antibody or a functional fragment thereof. In a preferred embodiment, said IL-1β binding antibody or a fragment thereof is canakinumab or a fragment thereof or gevokizumab or a fragment thereof. Similarly the level of hsCRP is possibly relevant in determining whether a patient with cancer having at least a partial inflammatory basis, diagnosed or undiagnosed, should be treated with an IL-1β inhibitor, IL-1β binding antibody or a functional fragment thereof. In a preferred embodiment, said IL-1β binding antibody is canakinumab or gevokizumab.

[0347] Thus the present invention provides high sensitivity C-reactive protein (hsCRP) for use as a biomarker in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, in a patient with an IL-1β inhibitor, IL-1β binding antibody or a functional fragment thereof, wherein said patient is eligible for the treatment and/or prevention if the level of high sensitivity C-reactive protein (hsCRP) is equal to or higher than 2 mg/L, or equal to or higher than 3 mg/L, or equal to or higher than 4 mg/L, or equal to or higher than 5 mg/L, or equal to or higher than 6 mg/L, equal to or higher than 7 mg/L, equal to or higher than 8 mg/L, equal to or higher than 9 mg/L, or equal to or higher than 10 mg/L, equal to or higher than 12 mg/L, equal to or higher than 15 mg/L, equal to or higher than 20 mg/L or equal to or higher than 25 mg/L as assessed prior to the administration of the IL-1β binding antibody or a functional fragment thereof. In a preferred embodiment, said patient has hsCRP level equal to or higher than 4 mg/L. In a preferred embodiment, said patient has hsCRP level equal to or higher than 6 mg/L. In a preferred embodiment, said patient has hsCRP level equal to or higher than 10 mg/L.

[0348] In analyses of combined canakinumab doses, compared to placebo, the observed hazard ratio for lung cancer among those who achieved hsCRP reductions greater than the median value of 1.8 mg/L at 3 months was 0.29 (95% CI 0.17-0.51, P<0.0001), better than the effect observed for those who achieved hsCRP reductions less than the median value (HR 0.83, 95% CI 0.56-1.22, P=0.34).

[0349] Thus in one aspect, the present invention relates to the use of the degree of reduction of the hsCRP as a prognostic biomarker to guide physician in continuing or discontinuing with the treatment of an IL-1β inhibitor, an IL-1β binding antibody or a functional fragment thereof, especially canakinumab or gevokizumab. In one embodiment, the present invention provides the use of an IL-1β inhibitor, an IL-1β binding antibody or a functional fragment thereof, in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, wherein such treatment or prevention is continued when the level of hsCRP is reduced by at least 0.8 mg/L, at least 1 mg/L, at least 1.2 mg/L, at least 1.4 mg/L, at least 1.6 mg/L, at least 1.8 mg/L, at least 3 mg/L or at least 4 mg/L, at least 3 months, preferably 3 months after first administration of the IL-1β binding antibody or functional fragment thereof. In one embodiment, the present invention provides the use of an IL-1β inhibitor, IL-1β binding antibody or a functional fragment thereof, in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer, wherein such treatment or prevention is discontinued when the level of hsCRP is reduced by less than 0.8 mg/L, less than 1 mg/L, less than 1.2 mg/L, less than 1.4 mg/L, less than 1.6 mg/L, less than 1.8 mg/L at about 3 months from the beginning of the treatment at an appropriate dosing with the IL-1β binding antibody or functional fragment thereof. In a further embodiment the appropriate dosing of canakinumab is 50 mg, 150 mg or 300 mg, which is administered every 3 months. In a further embodiment the appropriate dosing of canakinumab is 300 mg administered twice over a two-week period and then every three months. In one embodiment, the IL-1β binding antibody or a functional fragment thereof is canakinumab or a functional fragment thereof, wherein said canakinumab is administered at a dose of 200 mg every 3 weeks or 200 mg monthly. In one embodiment, the IL-1β binding antibody or a functional fragment thereof is gevokizumab or a functional fragment thereof, wherein said gevokizumab is administered at a dose of 60 mg to 90 mg or 120 mg every 3 weeks or monthly.

[0350] In one aspect, the present invention provides the use of the reduced hsCRP level as a prognostic biomarker to guide a physician in continuing or discontinuing with the treatment of an IL-1β binding antibody or a functional fragment thereof, especially canakinumab or gevokizumab. In one embodiment, such treatment and/or prevention with the IL-1β binding antibody or a functional fragment thereof is continued when the level of hsCRP is reduced below 10 mg, reduced below 8 mg/L, reduced below 5 mg/L, reduced below 3.5 mg/L, below 3 mg/L, below 2.3 mg/L, below 2 mg/L or below 1.8 mg/L assessed at least 3 months from first administration of the IL-1β binding antibody or a functional fragment thereof. In one embodiment, such treatment and/or prevention with the IL-1β binding antibody or a functional fragment thereof is discontinued when the level of hsCRP is not reduced below 3.5 mg/ml, below 3 mg/L, below 2.3 mg/L, below 2 mg/L or below 1.8 mg/L assessed at least 3 months from first administration of the IL-1β binding antibody or a functional fragment thereof. In a further embodiment the appropriate dosing is canakinumab at 300 mg administered twice over a two-week period and then every

three months. In one embodiment, the IL-1β binding antibody or a functional fragment thereof is canakinumab or a functional fragment thereof, wherein said canakinumab is administered at a dose of 200 mg every 3 weeks or 200 mg monthly or 300 mg monthly. In one embodiment, the IL-1β binding antibody or a functional fragment thereof is gevokizumab or a functional fragment thereof, wherein said gevokizumab is administered at a dose of 60 mg to 90 mg or 120 mg every 3 weeks or monthly.

[0351] In one aspect, the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis, wherein said IL-1β binding antibody or a functional fragment thereof is administered at a dose sufficient to inhibit angiogenesis in said patient. Without wishing to be bound by theory, it is hypothesized that the inhibition of IL-1β pathway can lead to inhibition or reduction of angiogenesis, which is a key event for tumor growth and for tumor metastasis. Thus in clinical settings the inhibition of angiogenesis can be measured by tumor shrinkage, no tumor growth (stable disease), prevention of metastasis or delay of metastasis. Typically cancer having at least partial inflammatory basis includes but is not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, multiple myeloma and pancreatic cancer.

[0352] In one embodiment said cancer is lung cancer, especially NSCLC. In one embodiment said cancer is breast cancer. In one embodiment said cancer is colorectal cancer. In one embodiment said cancer is gastric cancer. In one embodiment said cancer is renal carcinoma. In one embodiment said cancer is melanoma.

[0353] In one embodiment said dose sufficient to inhibit angiogenesis comprises an IL-1β binding antibody or a functional fragment thereof to be administered in the range of about 30 mg to about 750 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, preferably 150 mg to 300 mg; alternatively at least 150 mg, at least 180 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with a cancer that has at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every three weeks, every four weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the range of DRUG of the invention is 90 mg to 450 mg. In one embodiment said DRUG of the invention is administered monthly. In one embodiment said DRUG of the invention is administered every 3 weeks.

[0354] In one embodiment, the IL-1β binding antibody is canakinumab administered at a dose sufficient to inhibit angiogenesis, wherein said dose is in the range of about 100 mg to about 750 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, alternatively at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with cancer having at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every 3 weeks, every 4 weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the patient with lung cancer receives canakinumab monthly. In one embodiment the preferred dose range of canakinumab is 200 mg to 450 mg, further preferred 300 mg to 450 mg, further preferred 350 mg to 450 mg. In one embodiment the preferred dose range of canakinumab is 200 mg to 450 mg every 3 weeks or monthly. In one embodiment the preferred dose of canakinumab is 200 mg every 3 weeks. In one embodiment the preferred dose of canakinumab is 200 mg monthly. In one embodiment canakinumab is administered subcutaneously or intravenously, preferably subcutaneously.

[0355] In one embodiment, the IL-1β binding antibody is gevokizumab administered at a dose sufficient to inhibit angiogenesis, wherein said dose is in the range of about 30 mg to about 450 mg per treatment, alternatively 90 mg-450 mg, 90 mg to 360 mg, 90 mg to 270 mg, 90 mg to 180 mg; alternatively 120 mg-450 mg, 120 mg to 360 mg, 120 mg to 270 mg, 120 mg to 180 mg, alternatively 150 mg-450 mg, 150 mg to 360 mg, 150 mg to 270 mg, 150 mg to 180 mg; alternatively 180 mg-450 mg, 180 mg to 360 mg, 180 mg to 270 mg; alternatively at least 150 mg, at least 180 mg, at least 240 mg, at least 270 mg per treatment. In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives treatment every 2 weeks, every 3 weeks, monthly, every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives at least one, preferably one treatment per month. In one embodiment the preferred range of gevokizumab is 150 mg to 270 mg. In one embodiment the preferred range of gevokizumab is 60 mg to 180 mg, further preferred 60 mg to 90 mg. In one embodiment the preferred schedule is every 3 weeks. In one embodiment the preferred schedule is monthly. In one embodiment the patient receives gevokizumab 60 mg to 90 mg every 3 weeks. In one embodiment the patient receives gevokizumab 60 mg to 90 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg every 3 weeks. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg monthly. In one embodiment the patient receives gevokizumab 90 mg, every 180 mg, 190 mg or 200 mg every 3 weeks. In one embodiment the patient receives gevokizumab 90 mg, every 180 mg, 190 mg or 200 mg monthly. In one embodiment the patient receives gevokizumab 120 mg monthly or every 3 weeks. In one embodiment gevokizumab is administered subcutaneously or intravenously, preferably intravenously.

[0356] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the embodiment of angiogenesis inhibition. In one preferred embodiment IL-1β antibody or a functional fragment thereof is used in combination of one or more chemotherapeutic agents, wherein said agent is an anti-Wnt inhibitor, preferably Vantictumab.

[0357] Without wishing to be being bound by theory, it is hypothesized that the inhibition of IL-1β pathway can lead to inhibition or reduction of tumor metastasis. Until now there have been no reports on the effects of canakinumab on

metastasis. Data presented in example 3 demonstrate that IL-1β activates different pro-metastatic mechanisms at the primary site compared with the metastatic site: Endogenous production of IL-1β by breast cancer cells promotes epithelial to mesenchymal transition (EMT), invasion, migration and organ specific homing. Once tumor cells arrive in the bone environment contact between tumor cells and osteoblasts or bone marrow cells increase IL-1β secretion from all three cell types. These high concentrations of IL-1β cause proliferation of the bone metastatic niche by stimulating growth of disseminated tumor cells into overt metastases. These pro-metastatic processes are inhibited by administration of anti-IL-1β treatments, such as canakinumab.

[0358] Therefore, targeting IL-1β with an IL-1β binding antibody represents a novel therapeutic approach for cancer patients at risk of progressing to metastasis by preventing seeding of new metastases from established tumors and retaining tumor cells already disseminated in the bone in a state of dormancy. The models described have been designed to investigate bone metastasis and although the data show a strong link between IL-1β expression and bone homing, it does not exclude IL-1β involvement in metastasis to other sites.

[0359] Accordingly, in one aspect, the present invention provides an IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis, wherein said IL-1β binding antibody or a functional fragment thereof is administered at a dose sufficient to inhibit metastasis in said patient. Typically cancer having at least partial inflammatory basis includes but is not limited to lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, multiple myeloma and pancreatic cancer.

[0360] In one embodiment said dose sufficient to inhibit metastasis comprises an IL-1β binding antibody or a functional fragment thereof to be administered in the range of about 30 mg to about 750 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, preferably 150 mg to 300 mg; alternatively at least 150 mg, at least 180 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with a cancer that has at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every three weeks, every four weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the range of DRUG of the invention is 90 mg to 450 mg. In one embodiment said DRUG of the invention is administered monthly. In one embodiment said DRUG of the invention is administered every 3 weeks.

[0361] In one embodiment the IL-1β binding antibody is canakinumab administered at a dose sufficient to inhibit metastasis, wherein said dose is in the range of about 100 mg to about 750 mg per treatment, alternatively 100 mg-600 mg, 100 mg to 450 mg, 100 mg to 300 mg, alternatively 150 mg-600 mg, 150 mg to 450 mg, 150 mg to 300 mg, alternatively at least 150 mg, at least 200 mg, at least 250 mg, at least 300 mg per treatment. In one embodiment the patient with cancer having at least a partial inflammatory basis, including lung cancer, receives each treatment every 2 weeks, every 3 weeks, every 4 weeks (monthly), every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the patient with cancer receives canakinumab monthly. In one embodiment the preferred dose range of canakinumab is 200 mg to 450 mg, further preferred 300 mg to 450 mg, further preferred 350 mg to 450 mg. In one embodiment the preferred dose range of canakinumab is 200 mg to 450 mg every 3 weeks or monthly. In one embodiment the preferred dose of canakinumab is 200 mg every 3 weeks. In one embodiment the preferred dose of canakinumab is 200 mg monthly. In one embodiment canakinumab is administered subcutaneously or intravenously, preferably subcutaneously.

[0362] In one embodiment, the IL-1β binding antibody is gevokizumab administered at a dose sufficient to inhibit metastasis, wherein said dose is in the range of about 30 mg to about 450 mg per treatment, alternatively 90 mg-450 mg, 90 mg to 360 mg, 90 mg to 270 mg, 90 mg to 180 mg; alternatively 120 mg-450 mg, 120 mg to 360 mg, 120 mg to 270 mg, 120 mg to 180 mg, alternatively 150 mg-450 mg, 150 mg to 360 mg, 150 mg to 270 mg, 150 mg to 180 mg; alternatively 180 mg-450 mg, 180 mg to 360 mg, 180 mg to 270 mg; alternatively at least 150 mg, at least 180 mg, at least 240 mg, at least 270 mg per treatment. In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives treatment every 2 weeks, every 3 weeks, monthly, every 6 weeks, bimonthly (every 2 months) or quarterly (every 3 months). In one embodiment the patient with cancer that has at least a partial inflammatory basis, including lung cancer, receives at least one, preferably one treatment per month. In one embodiment the preferred range of gevokizumab is 150 mg to 270 mg. In one embodiment the preferred range of gevokizumab is 60 mg to 180 mg, further preferred 60 mg to 90 mg. In one embodiment the preferred schedule is every 3 weeks. In one embodiment the preferred schedule is monthly. In one embodiment the patient receives gevokizumab 60 mg to 90 mg every 3 weeks. In one embodiment the patient receives gevokizumab 60 mg to 90 mg monthly. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg every 3 weeks. In one embodiment the patient with cancer that has at least a partial inflammatory basis receives gevokizumab about 90 mg to about 360 mg, 90 mg to about 270 mg, 120 mg to 270 mg, 90 mg to 180 mg, 120 mg to 180 mg, 120 mg or 90 mg monthly. In one embodiment the patient receives gevokizumab 90 mg, every 180 mg, 190 mg or 200 mg every 3 weeks. In one embodiment the patient receives gevokizumab 90 mg, every 180 mg, 190 mg or 200 mg monthly. In one embodiment the patient receives gevokizumab 120 mg monthly or every 3 weeks. In one embodiment gevokizumab is administered subcutaneously or intravenously, preferably intravenously.

[0363] All the disclosed uses throughout this application, including but not limited to, doses and dosing regimens, combinations, route of administration and biomarkers can be applied to the embodiment of metastasis inhibition. In one preferred embodiment IL-1β antibody or a functional fragment thereof is used in combination of one or more chemotherapeutic agents, wherein said agent is an anti-Wnt inhibitor, preferably Vantictumab.

[0364] IL-1β is known to drive the induction of gene expression of a variety of pro-inflammatory cytokines, such

as IL-6 and TNF-α. In the CANTOS trial, it was observed that administration of canakinumab was associated with dose-dependent reductions in IL-6 of 25 to 43 percent (all P-values<0.0001). The present invention therefore also provides an IL-6 inhibitor for use in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including but not limited to lung cancer. In some embodiments, the IL-6 inhibitor is selected from the group consisting of: anti-sense oligonucleotides against IL-6, IL-6 antibodies such as siltuximab (Sylvant®), sirukumab, clazakizumab, olokizumab, elsilimomab, gerilimzumab, WBP216 (also known as MEDI 5117), or a fragment thereof. EBI-031 (Eleven Biotherapeutics), FB-704A (Fountain BioPharma Inc), OP-R003 (Vaccinex Inc), IG61, BE-8, PPV-06 (Peptinov), SBP002 (Solbec), Trabectedin (Yondelis®), C326/AMG-220, olamkicept, PGE1 and its derivatives, PGI2 and its derivatives, and cyclophosphamide. Another embodiment of the present invention provides an IL-6 receptor (IL-6R) (CD126) inhibitor for use in the treatment and/or prevention of cancer having at least a partial inflammatory basis, including lung cancer. In some embodiments, the IL-6R inhibitor is selected from the group consisting of: anti-sense oligonucleotides against IL-6R, tocilizumab (Actemra®), sarilumab (Kevzara®), vobarilizumab, PM1, AUK12-20, AUK64-7, AUK146-15, MRA, satralizumab, SL-1026 (SomaLogic), LTA-001 (Common Pharma), BCD-089 (Biocad Ltd), APX007 (Apexigen/Epitomics), TZLS-501 (Novimmune), LMT-28, anti-IL-6R antibodies disclosed in WO2007143168 and WO2012118813, Madindoline A, Madindoline B, and AB-227-NA.

As used herein, canakinumab is defined under INN number 8836 and has the following sequence:

Light chain

(SEQ ID NO: 1007)

```
  1    EIVLTQSPDF QSVTPKEKVT ITCRASQSIG SSLHWYQQKP DQSPKLLIKY ASQSFSGVPS

 61    RFSGSGSGTD FTLTINSLEA EDAAAYYCHQ SSSLPFTFGP GTKVDIKRTV AAPSVFIFPP

121    SDEQLKSGTA SVVCLLNNFY PREAKVQWKV DNALQSGNSQ ESVTEQDSKD STYSLSSTLT

181    LSKADYEKHK VYACEVTHQG LSSPVTKSFN RGEC*
```

Heavy, chain:

(SEQ ID NO: 1008)

```
  1    QVQLVESGGG VVQPGRSLRL SCAASGFTFS VYGMNWVRQA PGKGLEWVAI IWYDGDNQYY

 61    ADSVKGRFTI SRDNSKNTLY LQMNGLRAED TAVYYCARDL RTGPFDYWGQ GTLVTVSSAS

121    TKGPSVFPLA PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL

181    YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS

241    VFLFPPKPKD TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST

301    YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY TLPPSREEMT

361    KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD SDGSFFLYSK LTVDKSRWQQ

421    GNVFSCSVMH EALHNHYTQK SLSLSPGK*
```

As used herein gevokizumab, which is defined under INN number 9310, has the following sequence

Heavy chain/Chaîne lourde/Cadena pesada

(SEQ ID NO: 1009)

```
QVQLQESGPG LVKPSQTLSL TCSFSGFSLS TSGMGVGWIR QPSGKGLEWL     50

AHIWWDGDES YNPSLKSRLT ISKDTSKNQV SLKITSVTAA DTAVYFCARN    100

RYDPPWFVDW GQGTLVTVSS ASTKGPSVFP LAPCSRSTSE STAALGCLVK    150

DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VTSSNFGTQT    200

YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF LFPPKPKDTL    250

MISRTPEVTC VVVDVSHEDP EVQFNWYVDG MEVHNAKTKP REEQFNSTFR    300

VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG QPREPQVYTL    350

PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPMLDSD    400

GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG         445
```

-continued

Light chain/Chaîne légère/Cadena ligera

(SEQ ID NO: 1010)

DIQMTQSTSS LSASVGDRVT ITCRASQDIS NYLSWYQQKP GKAVKLLIYY 50

TSKLHSGVPS RFSGSGSGTD YTLTISSLQQ EDFATYFCLQ GKMLPWTFGQ 100

GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200

LSSPVTKSFN RGEC 214

[0365] By "IL-1β binding antibody" is meant any antibody capable of binding to the IL-1β specifically and consequently inhibiting or modulating the binding of IL-1β to its receptor and further consequently inhibiting IL-1β function.

[0366] As used herein, the term "functional fragment" of an antibody as used herein, refers to portions or fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., IL-1β). Examples of binding fragments encompassed within the term "functional fragment" of an antibody include single chain Fv (scFv), a Fab fragment, a monovalent fragment consisting of the V_L, V_H, CL and CH1 domains; a F(ab)2 fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; a Fd fragment consisting of the V_H and CH1 domains; a Fv fragment consisting of the V_L and V_H domains of a single arm of an antibody; a dAb fragment (Ward et al., 1989), which consists of a VH domain; and an isolated complementarity determining region (CDR).

[0367] Other features, objects, and advantages of the invention will be apparent from the description and drawings, and from the claims.

[0368] The following Examples illustrate the invention described above; they are not, however, intended to limit the scope of the invention in any way.

EXAMPLE

[0369] The Example below is set forth to aid in the understanding of the invention but is not intended, and should not be construed, to limit its scope in any way.

Example 1

[0370] A Phase III, Multicenter, Randomized, Double Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Canakinumab Versus Placebo as Adjuvant Therapy in Adult Subjects with Stages II-IIIA and IIIB (T>5 cm N2) Completely Resected (R0) Non-Small Cell Lung Cancer (NSCLC)

[0371] The purpose of this prospective, multicenter, randomized, double blind, placebo-controlled phase III study is to evaluate the efficacy and safety of canakinumab as adjuvant therapy, following standard of care for completely resected (R0) AJCC/UICC v. 8 stages II-IIIA and stage IIIB (T>5 cm N2) NSCLC subjects.

Study Design

[0372] This phase III study CACZ885T2301 (FIG. **20**) will enroll adult subjects with completely resected (R0) NSCLC AJCC/UICC v. 8 stages II-IIIA and IIIB (T>5 cm and N2) disease. Subjects will complete standard of care adjuvant treatments for their NSCLC, including cisplatin-based chemotherapy and mediastinal radiation therapy (if applicable), before being screened or randomized for this study. Subjects may be screened after undergoing complete surgical resection of their NSCLC and having R0 status confirmed (negative margins on pathologic review), after completing adjuvant cisplatin-based doublet chemotherapy if applicable, (and, if applicable, radiation therapy for stage IIIA N2 or IIIB N2 disease) and after all entry criteria are met. Subjects must not have had preoperative neo-adjuvant chemotherapy or radiotherapy to achieve the R0 status. Approximately 1500 subjects will be randomized 1:1 to canakinumab or matching placebo.

Dosing Regimen

[0373] The study is double-blind. All eligible subjects will be randomized to one of the following two treatment arms in a 1:1 ratio:

Canakinumab 200 mg s.c. on day 1 of every 21-day cycle for 18 cycles

Placebo s.c. on day 1 of every 21-day cycle for 18 cycles

[0374] Randomization will be stratified by AJCC/UICC v. 8 stage: IIA versus IIB versus IIIA versus IIIB with T>5 cm, N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW). Subjects will continue their assigned treatment until they complete 18 cycles or experience any one of the following: disease recurrence as determined by Investigator, unacceptable toxicity that precludes further treatment, treatment discontinuation at the discretion of the Investigator or subject, or death, or lost to follow-up, whichever occurs first. It is postulated that the one year duration of adjuvant treatment will provide an acceptable benefit in subjects who have intermediate or high risk of developing disease recurrence. If disease recurrence is not observed during the treatment phase, subjects will be followed until disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death or the sponsor terminates the study for up to five years. All subjects who discontinue from the study treatment will be followed up every 12 weeks for survival until the final overall survival (OS) analysis or death, lost to follow-up or withdrawal of consent for survival follow-up.

[0375] Standard of care includes complete resection of the NSCLC with margins free of cancer. Four cycles of cisplatin-based doublet chemotherapy are required for all stage IIB-IIIA and IIIB (T>5 cm N2) disease subjects (except if not tolerated, in which case at least 2 cycles of adjuvant chemotherapy are required); chemotherapy is recommended but not mandatory for stage IIA with T (>4-5 cm). Radiation therapy to mediastinal nodes is suggested but not required for all stage IIIA N2 and IIIB (T>5 cm N2) disease subjects. All subjects must have had complete surgical resection of

their NSCLC to be eligible for study entry; and margins must be pathologically reviewed and documented as negative. Comparisons will be made between the arms for efficacy: DFS, OS, LCSS and Quality of Life measures (EQ-5D-5L and EORTC QLQ-C30/LC13) and for safety.

[0376] Detection of first disease recurrence will be done by clinical evaluation that includes physical examination, and radiological tumor measurements as determined by the investigator. In case of non-conclusive radiological evidence, a biopsy should be performed to confirm recurrence. The following assessments are required at screening/baseline: Chest, abdomen and pelvis CT or MRI, brain MRI and whole body bone scan, if clinically indicated. Subsequent imaging assessments will be done every 12 weeks (±7 days) for the first year (treatment phase) following Cycle 1 Day 1, then every 26 weeks during years two and three, and annually during years four and five (post-treatment surveillance phase). The intervals between imaging assessments across all study phases should be respected as described above regardless of whether study treatment is temporarily withheld or permanently discontinued before the last scheduled dose administration on Cycle 18 Day 1, or if unscheduled assessments are performed. If a subject discontinues study treatment for reasons other than recurrence, recurrence assessments should continue as per the scheduled visits until disease recurrence, withdrawal of consent by the subject, subject is lost to follow up, death, or the sponsor terminates the study.

Primary Objective and Key Secondary Objective:

Primary Objective

[0377] The primary objective is to compare the Disease-free survival (DFS) in the canakinumab versus placebo arms as determined by local investigator assessment.

Statistical Hypothesis, Model, and Method of Analysis

[0378] Assuming proportional hazards model for DFS, the following statistical hypotheses will be tested to address the primary efficacy objective:

H01 (null hypotheses): $\Theta 1 \geq 0$ vs. Ha1 (alternative hypotheses): $\Theta 1 < 0$

Where $\Theta 1$ is the log hazard ratio of DFS in the canakinumab (investigational) arm vs. placebo (control) arm.

[0379] The primary efficacy analysis to test this hypothesis and compare the two treatment groups will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the following randomization stratification factors: AJCC/UICC v. 8 stage IIA versus IIB versus IIIA versus IIIB with T>5 cm N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW). The hazard ratio for DFS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for the log-rank test.

Key Secondary Objective

[0380] The key secondary objective is to determine whether treatment with canakinumab prolongs overall survival OS compared with placebo arm. OS is defined as the time from the date of randomization to the date of death due to any cause. If a subject is not known to have died, then OS will be censored at the latest date the subject was known to be alive (on or before the cut-off date). Assuming proportional hazards model for OS, the following statistical hypotheses will be tested only if DFS is statistically significant:

H02 (null hypotheses): $\Theta 2 \geq 0$ vs. Ha2 (alternative hypotheses): $\Theta 2 < 0$

Where $\Theta 2$ is the log hazard ratio of OS in the canakinumab (investigational) arm vs. placebo (control) arm. The analysis to test these hypotheses will consist of a stratified log-rank test at an overall one-sided 2.5% level of significance. The stratification will be based on the following randomization stratification factors: AJCC/UICC v. 8 stage IIA versus IIB versus IIIA versus IIIB T>5 cm N2 disease; Histology: squamous versus non-squamous; and Region: Western Europe and North America vs. eastern Asia vs. Rest of the world (RoW).

[0381] The OS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for OS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

Secondary Objectives

[0382] 1. To compare lung cancer specific survival in the canakinumab arm versus placebo arm:

[0383] Lung cancer specific survival (LCSS) is defined as the time from the date of randomization to the date of death due to lung cancer. Analyses will be based on the FAS population according to the randomized treatment group and strata assigned at randomization. The LCSS distribution will be estimated using the Kaplan-Meier method, and Kaplan-Meier curves, medians and 95% confidence intervals of the medians will be presented for each treatment group. The hazard ratio for LCSS will be calculated, along with its 95% confidence interval, using a stratified Cox model.

[0384] 2. To characterize the safety profile of canakinumab

[0385] Frequency of AEs, ECGs and laboratory abnormalities

[0386] 3. To characterize the pharmacokinetics of canakinumab therapy

[0387] Serum concentration-time profiles of canakinumab and appropriate individual PK parameters based on population PK model

[0388] 4. To characterize the prevalence and incidence of immunogenicity (antidrug antibodies, ADA) of canakinumab

[0389] Serum concentrations of anti-canakinumab antibodies

[0390] 5. To assess the effect of canakinumab versus placebo on PROs (EORTC QLQ-C30 with QLQ-LC13 incorporated and EQ-5D) including functioning and health-related quality of life Time to definitive 10 point deterioration symptom scores of pain, cough and dyspnea per QLQ-LC13 questionnaire are primary PRO variables of interest. Time to definitive deterioration in global health status/QoL, shortness of breath and pain per QLQ-C30 together with the utilities derived from EQ-5D-5L are secondary PRO variables of interest The European Organization for Research and Treatment of Cancer's core quality of life questionnaire EORTC-QLQC30 (version 3.0) and it's lung cancer specific module QLQLC13 (version 1.0) will be used to collect data

on the subject's functioning, disease-related symptoms, health-related quality of life, and health status. The EQ-5D-5L will be used for the purpose of the computation of utilities that can be used in health economic studies. The EORTC QLQ-C30/LC13 as well as the EQ-5D-5L are reliable and valid measures frequently used in clinical trials of subjects with lung cancer and previously used in the adjuvant setting (Bezjak et al 2008).

Example 2A

Blocking IL-1β Signaling Alters Blood Vessels in the Bone Microenvironment

[0391] Background: We have recently identified interleukin-1β (IL-1β) as a potential biomarker for predicting breast cancer patients at increased risk for developing bone metastasis. In addition we have shown that blocking IL-1β activity inhibits development of bone metastases from breast cancer cells disseminated in bone and reduces tumour angiogenesis. We hypothesise that interactions between IL-1β and IL-1R also promotes formation of new blood vessels in the bone microenvironment stimulating development of metastases at this site.

[0392] Objectives: Investigate the effects of blocking IL-1β activity on blood vessel formation within bone.

[0393] Methodology: The effects of IL-R inhibition on vasculature in trabecular bone were determined in mice treated with 1 mg/kg of the IL-1R antagonist (anakinra) for 21/31 days, the IL-1β antibody canakinumab (Ilaris) for 0-96 hours or in genetically engineered IL-1R1 knockout (KO) mice. Vasculature was visualised following CD34 and endomucin immunohistochemistry and the concentration of vascular endothelial growth factor (VEGF) and endothelin-1 in serum and/or bone marrow was determined by ELISA. Effects on bone volume were measured by Micro computed tomography (uCT).

[0394] Results: Canakinumab (Ilaris) caused a significant decrease in the length of new blood vessels from 0.09 mm (control) to 0.06 mm (24 hours Ilaris) (P=0.0319). IL-1R1 KO mice and mice treated with anakinra demonstrated a downwards trend in the average length of new blood vessels. Inhibition of IL-R resulted in increased trabecular bone volume. Anakinra caused a 69% decrease in the concentration of endothelin-1 in mice treated for 31 days (P=0.0269) and a 22% decrease in VEGF concentration in mice treated for 21 days (P=0.0104). Canakinumab (Ilaris) caused a 46% reduction in VEGF concentration and a 47% reduction in endothelin-1 concentration in mice treated for 96 hours.

[0395] Conclusions: These data demonstrate that IL-R activity plays an important role in the formation of new vasculature in bone and inhibiting its activity pharmacologically has potential as a novel treatment for breast cancer bone metastasis.

Example 2B

IL-1B Signalling Regulates Breast Cancer Bone Metastasis

[0396] Breast cancer bone metastases is incurable and associates with poor prognosis in patients. After homing and colonising the bone, breast cancer cells remain dormant, until signals from the microenvironment stimulate proliferation of these disseminated cells to form overt metastases. We have recently identified interleukin 1B (IL-1B) as a potential marker for predicting breast cancer patients at increased risk for developing metastasis and established a role for IL-1 signalling in tumour cell dormancy in bone. We hypothesise that tumour derived and microenvironment dependent IL-1B play major roles in breast cancer metastasis and growth in bone.

[0397] Here, we report our findings on the role of IL-1B signalling in breast cancer bone metastasis: Using a murine model of spontaneous human breast cancer metastasis to human bone, we found that administration of the clinically available anti-IL-1B monoclonal antibody, Ilaris, significantly reduced bone metastasis, while increasing primary tumour growth. Whereas, blockade of IL1R1 using a recombinant form of the receptor antagonist, Anakinra, delayed onset of breast cancer metastasis in human bone, without affecting the development of primary breast cancer. These finding suggest that IL1 signalling might exert different functions in breast cancer progression at the primary and metastatic site. Our data further highlight roles for both tumour derived and microenvironment derived IL-1 signalling in tumour cell dissemination and growth in bone: Inhibition of IL-1B/IL-1R1 with Ilaris or Anakinra reduced bone turnover and neovascularisation rendering the bone microenvironment less permissive for growth of breast cancer cells. In addition, overexpression of IL1B or IL1R in human breast cancer cells increased bone metastases from tumour cells injected directly into the circulation in vivo. These data demonstrate that IL-1B/IL-1R1 signalling plays an important role in the formation of bone metastasis and inhibiting its activity pharmacologically has potential as a novel treatment for breast cancer bone metastasis.

Example 2C

Targeting IL1b-Wnt Signalling Prevents Breast Cancer Colonisation in the Bone Microenvironment

[0398] Dissemination of tumour cells to bone marrow is an early event in breast cancer, however these cells may lie dormant in the bone environment for many years prior to eventual colonisation. Treatment for bone metastases is not curative, therefore new adjuvant therapies preventing disseminated cells from becoming metastatic lesions may be an effective therapeutic option to improve clinical outcomes. There is evidence that cancer stemcells (CSCs) within breast tumours are the cells capable of metastasis; however, little is known about which bone marrow-derived factors support dormant CSC survival and eventual colonisation. Using in vitro culture of primary human bone marrow and patient-derived breast cancer cells, and in vivo metastasis models of human breast cancer cells implanted into mice, we investigated signalling pathways regulating CSC colony formation in bone.

[0399] We demonstrate that exposure to the bone microenvironment stimulates breast CSC colony formation in 15/17 patient-derived early breast cancers in vitro, and promotes a 3-4-fold increase in colony formation in breast cancer cells injected intra-femorally in vivo (p\0.05). Further, we establish that IL1b secreted by human bone marrow induces breast CSC colony formation via intracellular NFkB signalling that induces Wnt secretion. Crucially, we show that inhibiting either IL1b (using an IL1b neutralising antibody or the IL1R antagonist Anakinra) or Wnt signalling (using Vantictumab, a therapeutic antibody which binds 5/10 Frizzled receptors), reverses induction of CSC activity by the bone marrow in vitro (Anakinra; p\0.0001, Vantictumab;

p\0.01) and prevents spontaneous bone metastasis in vivo (IL1b neutralising antibody; p\0.02, Vantictumab; p\0.01). These data indicate that IL-1b-Wnt inhibitors will prevent disseminated CSCs from forming metastatic colonies in bone, and represent an attractive adjuvant therapeutic opportunity in breast cancer. Drugs which target IL-1b (Anakinra and Canakinumab) are FDA-approved for other indications, and anti-Wnt treatments (Vantictumab) are in clinical trials in cancer, making this a viable therapeutic target in breast cancer patients.

Example 2C

Targeting IL-1β-Wnt Signalling to Prevent Breast Cancer Colonisation in the Bone Microenvironment

[0400] Dissemination of tumour cells to bone marrow is an early event in breast cancer, but these cells may lie dormant in the bone environment for many years before the development of clinical bone metastases. There is evidence that cancer stem cells (CSCs) within breast tumours are the cells capable of metastasis, but the effect of the bone environment on the regulation of CSCs has not been investigated. We used two models to study this: in vitro culture of primary human bone marrow and patient-derived breast cancer cells, and in vivo intra-femoral injections of luciferase/tdTomato-labelled breast cancer cells into immune-deficient mice. CSC activity following isolation from the bone environment was measured using mammosphere colony formation.

[0401] We demonstrate that exposure to the bone microenvironment stimulates breast CSC colony formation in 15/17 patient-derived early breast cancers in vitro, and promotes a 3-4-fold increase in colony formation in breast cancer cells injected into the femoral bone marrow of mice in vivo ($p<0.05$). Furthermore, we establish that IL1b secreted by human bone marrow induces breast CSC colony formation via an induction of Wnt signalling in breast cancer cells. We show that inhibiting IL1β (using an IL1β neutralising antibody or the IL1R antagonist Anakinra) or Wnt signalling (using Vantictumab, a therapeutic antibody which binds 5/10 Frizzled receptors), reverses induction of CSC activity by the bone marrow in vitro (Anakinra; $p<0.0001$, Vantictumab; $p<0.01$), and prevents spontaneous bone metastasis in vivo (IL1β neutralising antibody, $p<0.02$, Vantictumab; $p<0.01$).

[0402] These data indicate that IL-1β-Wnt inhibitors may prevent disseminated CSCs from forming metastatic colonies in the bone, and should be considered as an adjuvant therapeutic opportunity in breast cancer. Clinically available drugs against IL-1β (Anakinra and Canakinumab) are licensed for other applications, and anti-Wnt treatments (Vantictumab) are in clinical trials, making this pathway a viable therapeutic target in breast cancer patients.

Example 2D

Anti-IL1B Therapy and Standard of Care Agents: A Double Edged-Sword to Halt Breast Cancer Bone Metastasis

[0403] Breast cancer bone metastases is incurable and associates with poor prognosis in patients. After homing and colonising the bone, breast cancer cells remain dormant, until signals from the microenvironment stimulate proliferation of these disseminated cells to form overt metastases. We have recently identified interleukin 1B (IL-1B) as a potential marker for predicting breast cancer patients at increased risk for developing metastasis and established a role for IL-1 signalling in tumour cell dormancy in bone. We hypothesise that tumour-derived and microenvironment-dependent IL-1B play major roles in breast cancer metastasis and growth in bone.

[0404] Here, we report our findings on the role of IL-1B signalling in breast cancer bone metastasis. Using a murine model of spontaneous human breast cancer metastasis to human bone, we found that administration of the clinically available anti-IL-1B monoclonal antibody, Ilaris, or the clinically available recombinant form of the receptor antagonist, Anakinra, reduced bone metastasis (photons/sec mean values: 3.60E+06 Placebo, 4.83E+04 Anakinra, 6.01E+04 Ilaris). In line with this finding, IL-1B or IL-1R1 overexpression in human breast cancer cells resulted in enhanced tumour cell dissemination and growth in bone (12.5, 75 and 50% animals with tumour in bone in control, IL-1B and IL-1R-overexpressing cells, respectively). The use of standard of care agents and/or anti-resorptive drugs is a treatment strategy for patients affected by breast cancer. Here, we combine anti-IL 1B treatment (Anakinra) with standard of care agent (Doxorubicin) and/or anti-resorptive agent (Zoledronic acid) in a syngeneic model of breast cancer metastasis. Our experiments show that the triple treatment significantly impairs breast cancer metastasis ($p=0.0084$).

[0405] In conclusion, these data demonstrate that IL-1B/IL-1R1 signalling plays an important role in the formation of bone metastasis and inhibiting its activity pharmacologically alone or in combination with standard of care therapies has potential as a novel treatment for bone metastasis.

Example 3

Tumor-Derived IL-1β Induces Differential Tumor Promoting Mechanisms in Metastasis

Materials and Methods

Cell Culture

[0406] Human breast cancer MDA-MB-231-Luc2-TdTomato (Calliper Life Sciences, Manchester UK), MDA-MB-231 (parental) MCF7, T47D (European Collection of Authenticated Cell Cultures (ECACC)), MDA-MB-231-IV (Nutter et al., 2014) as well as bone marrow HS5 (ECACC) and human primary osteoblasts OB1 were cultured in DMEM+10% FCS (Gibco, Invitrogen, Paisley, UK). All cell lines were cultured in a humidified incubator under 5% C02 and used at low passage>20.

Transfection of Tumor Cells:

[0407] Human MDA-MB-231, MCF 7 and T47D cells were stably transfected to overexpress genes IL1B or IL1R1 using plasmid DNA purified from competent *E. Coli* that have been transduced with an ORF plasmid containing human IL1B or IL1R1 (Accession numbers NM_000576 and NM_0008777.2, respectively) with a C-terminal GFP tag (OriGene Technologies Inc. Rockville Md.). Plasmid DNA purification was performed using a PureLink™ HiPure Plasmid Miniprep Kit (ThemoFisher) and DNA quantified by UV spectroscopy before being introduced into human cells with the aid of Lipofectamine II (ThermoFisher). Control cells were transfected with DNA isolated from the same plasmid without IL-1B or IL-1R1 encoding sequences.

In Vitro Studies

[0408] In vitro studies were carried out with and without addition of 0-5 ng/ml recombinant IL-1β (R&D systems, Wiesbaden, Germany)+/−50 μM IL-1Ra (Amgen, Cambridge, UK). Cells were transferred into fresh media with 10% or 1% FCS. Cell proliferation was monitored every 24h for up to 120h by manual cell counting using a 1/400 mm^2 hemocytometer (Hawkley, Lancing UK) or over a 72h period using an Xcelligence RTCA DP Instrument (Acea Biosciences, Inc). Tumor cell invasion was assessed using 6 mm transwell plates with an 8 μm pore size (Corning Inc) with or without basement membrane (20% Matrigel; Invitrogen). Tumor cells were seeded into the inner chamber at a density of 2.5×10^5 for parental as well as MDA-MB-231 derivatives and 5×10^5 for T47D in DMEM+1% FCS and 5×10^5 OB1 osteoblast cells supplemented with 5% FCS were added to the outer chamber. Cells were removed from the top surface of the membrane 24h and 48h after seeding and cells that had invaded through the pores were stained with hematoxylin and eosin (H&E) before being imaged on a Leica DM7900 light microscope and manually counted.

[0409] Migration of cells was investigated by analyzing wound closure: Cells were seeded onto 0.2% gelatine in 6-well tissue culture plates (Costar; Corning, Inc) and, once confluent, 10 μg/ml mitomycin C was added to inhibit cell proliferation and a 50 μm scratch made across the monolayer. The percentage of wound closure was measured at 24h and 48h using a CTR7000 inverted microscope and LAS-AF v2.1.1 software (Leica Applications Suite; Leica Microsystems, Wetzlar, Germany). All proliferation, invasion and migration experiments were repeated using the Xcelligence RTCA DP instrument and RCTA Software (Acea Biosystems, Inc).

[0410] For co-culture studies with human bone 5×10^5 MDA-MB-231 or T47D cells were seeded onto tissue culture plastic or into 0.5 cm^3 human bone discs for 24h. Media was removed and analysed for concentration of IL-1β by ELISA. For co-culture with HS5 or OB1 cells, 1×10^5 MDA-MB-231 or T47D cells were cultured onto plastic along with 2×10^5 HS5 or OB1 cells. Cells were sorted by FACS 24h later and counted and lysed for analysis of IL-1β concentration. Cells were collected, sorted and counted every 24h for 120h.

Animals

[0411] Experiments using human bone grafts were carried out in 10-week old female NOD SCID mice. In IL-1β/IL-1R1 overexpression bone homing experiments 6 to 8-week old female BALB/c nude mice were used. To investigate effects of IL-1β on the bone microenvironment 10-week old female C57BL/6 mice (Charles River, Kent, UK) or IL-$1R1^{-/-}$ mice (Abdulaal et al., 2016) were used. Mice were maintained on a 12h: 12h light/dark cycle with free access to food and water. Experiments were carried out with UK home office approval under project licence 40/3531, University of Sheffield, UK.

Patient Consent and Preparation of Bone Discs

[0412] All patients provided written, informed consent prior to participation in this study. Human bone samples were collected under HTA licence 12182, Sheffield Musculoskeletal Biobank, University of Sheffield, UK. Trabecular bone cores were prepared from the femoral heads of female patients undergoing hip replacement surgery using an Isomat 4000 Precision saw (Buehler) with Precision diamond wafering blade (Buehler). 5 mm diameter discs were subsequently cut using a bone trephine before storing in sterile PBS at ambient temperature.

In Vivo Studies

[0413] To model human breast cancer metastasis to human bone implants two human bone discs were implanted subcutaneously into 10-week old female NOD SCID mice (n=10/group) under isofluorane anaesthetic. Mice received an injection of 0.003 mg vetergesic and Septrin was added to the drinking water for 1 week following bone implantation. Mice were left for 4 weeks before injecting 1×10^5 MDA-MB-231 Luc2-TdTomato, MCF7 Luc2 or T47D Luc2 cells in 20% Martigel/79% PBS/1% toluene blue into the two hind mammary fat pads. Primary tumor growth and development of metastases was monitored weekly using an IVIS (Luminol) system (Caliper Life Sciences) following sub-cutaneous injection of 30 mg/ml D-luciferin (Invitrogen). On termination of experiments mammary tumors, circulating tumor cells, serum and bone metastases were resected. RNA was processed for downstream analysis by real time PCR, and cell lysates were taken for protein analysis and whole tissue for histology as previously described (Nutter et al., 2014; Ottewell et al., 2014a).

[0414] For therapeutic studies in NOD SCID mice, placebo (control), 1 mg/kg IL-1Ra (Anakinra®) daily or 10 mg/kg canakinumab subcutaneously every 14 days were administered starting 7 days after injection of tumor cells. In BALB/c mice and C57BL/6 mice 1 mg/kg IL-1Ra was administered daily for 21 or 31 days or 10 mg/kg canakinumab was administered as a single subcutaneous injection. Tumor cells, serum, and bone were subsequently resected for downstream analysis.

[0415] Bone metastases were investigated following injection of 5×10^5 MDA-MB-231 GFP (control), MDA-MB-231-IV, MDA-MB-231-IL-1B-positive or MDA-MB-231-IL-1R1-positive cells into the lateral tail vein of 6 to 8-week old female BALB/c nude mice (n=12/group). Tumor growth in bones and lungs was monitored weekly by GFP imaging in live animals. Mice were culled 28 days after tumor cell injection at which timepoint hind limbs, lungs and serum were resected and processed for microcomputed tomography imaging (μCT), histology and ELISA analysis of bone turnover markers and circulating cytokines as described (Holen et al., 2016).

Isolation of Circulating Tumor Cells

[0416] Whole blood was centrifuged at 10,000 g for 5 minutes and the serum removed for ELISA assays. The cell pellet was re-suspended in 5 ml of FSM lysis solution (Sigma-Aldrich, Pool, UK) to lyse red blood cells. Remaining cells were re-pelleted, washed 3× in PBS and re-suspended in a solution of PBS/10% FCS. Samples from 10 mice per group were pooled prior to isolation of TdTomato positive tumor cells using a MoFlow High performance cell sorter (Beckman Coulter, Cambridge UK) with the 470 nM laser line from a Coherent I-90C tenable argon ion (Coherent, Santa Clara, Calif.). TdTomato fluorescence was detected by a 555LP dichroic long pass and a 580/30 nm band pass filter. Acquisition and analysis of cells was performed using Summit 4.3 software. Following sorting

cells were immediately placed in RNA protect cell reagent (Ambion, Paisley, Renfrew, UK) and stored at −80 □ before RNA extraction.

Microcomputed Tomography Imaging:

[0417] Microcomputed tomography (μCT) analysis was carried out using a Skyscan 1172 x-ray-computed μCT scanner (Skyscan, Aartselar, Belgium) equipped with an x-ray tube (voltage, 49 kV; current, 200 uA) and a 0.5-mm aluminium filter. Pixel size was set to 5.86 μm and scanning initiated from the top of the proximal tibia as previously described (Ottewell et al., 2008a; Ottewell et al., 2008b).

Bone Histology and Measurement of Tumor Volume:

[0418] Bone tumor areas were measured on three non-serial, H&E stained, 5 μm histological sections of decalcified tibiae per mouse using a Leica RMRB upright microscope and Osteomeasure software (Osteometrics, Inc. Decauter, USA) and a computerised image analysis system as previously described (Ottewell et al., 2008a).

Western Blotting:

[0419] Protein was extracted using a mammalian cell lysis kit (Sigma-Aldrich. Poole, UK). 30 μg of protein was run on 4-15% precast polyacrylamide gels (BioRad, Watford, UK) and transferred onto an Immobilon nitrocellulose membrane (Millipore). Non-specific binding was blocked with 1% casein (Vector Laboratories) before incubation with rabbit monoclonal antibodies to human N-cadherin (D4R1H) at a dilution of 1:1000, E-cadherin (24E10) at a dilution of 1:500 or gamma-catenin (2303) at a dilution of 1:500 (Cell signalling) or mouse monoclonal GAPDH (ab8245) at a dilution of 1:1000 (AbCam, Cambridge UK) for 16h at 4□. Secondary antibodies were anti-rabbit or anti-mouse horse radish peroxidase (HRP; 1:15,000) and HRP was detected with the Supersignal chemiluminescence detection kit (Pierce). Band quantification was carried out using Quantity Once software (BioRad) and normalised to GAPDH.

Gene Analysis

[0420] Total RNA was extracted using an RNeasy kit (Qiagen) and reverse transcribed into cDNA using Superscript III (Invitrogen AB). Relative mRNA expression of IL-1B (Hs02786624), IL-1R1 (Hs00174097), CASP (Caspase 1) (Hs00354836), IL1RN (Hs00893626), JUP (junction plakoglobin/gamma-catenin) (Hs00984034), N-cadherin (Hs01566408) and E-cadherin (Hs1013933) were compared with the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH: Hs02786624) and assessed using an ABI 7900 PCR System (Perkin Elmer, Foster City, Calif.) and Taqman universal master mix (Thermofisher, UK). Fold change in gene expression between treatment groups was analysed by inserting CT values into Data Assist V3.01 software (Applied Biosystems) and changes in gene expression were only analysed for genes with a CT value of ≤25.

Assessment of IL-1β and IL-1R1 in Tumors from Breast Cancer Patients

[0421] IL-1β and IL-1R1 expression was assessed on tissue microarrays (TMA) containing primary breast tumor cores taken from 1,300 patients included in the clinical trial, AZURE (Coleman et al. 2011). Samples were taken pre-treatment from patients with stage II and III breast cancer without evidence of metastasis. Patients were subsequently randomized to standard adjuvant therapy with or without the addition of zoledronic acid for 10 years (Coleman et al 2011). The TMAs were stained for IL-1β (ab2105, 1:200 dilution, Abcam) and IL-1R1 (ab59995, 1:25 dilution, Abcam) and scored blindly under the guidance of a histopathologist for IL-1β/IL-1R1 in the tumor cells or in the associated stroma. Tumor or stromal IL-1β or IL-1R1 was then linked to disease recurrence (any site) or disease recurrence specifically in bone (+/−other sites).

The IL-1β Pathway is Upregulated During the Process of Human Breast Cancer Metastasis to Human Bone.

[0422] A mouse model of spontaneous human breast cancer metastasis to human bone implants was utilised to investigate how the IL-1β pathway changes through the different stages of metastasis. Using this model, the expression levels of genes associated with the IL-1β pathway increased in a stepwise manner at each stage of the metastatic process in both triple negative (MDA-MB-231) and estrogen receptor positive (ER+ve) (T47D) breast cancer cells: Genes associated with the IL-1β signalling pathway (IL-1B, IL-1R1, CASP (Caspase 1) and IL-1Ra) were expressed at very low levels in both MDA-MB-231 and T47D cells grown in vitro and expression of these genes were not altered in primary mammary tumors from the same cells that did not metastasize in vivo (FIG. **7**, panel a).

[0423] IL-1B, IL-1R1 and CASP were all significantly increased in mammary tumors that subsequently metastasized to human bone compared with those that did not metastasize ($p<0.01$ for both cell lines), leading to activation of IL-1β signalling as shown by ELISA for the active 17 kD IL-1β (FIG. **7**, panel b; FIG. **8**). IL-1B gene expression increased in circulating tumor cells compared with metastatic mammary tumors ($p<0.01$ for both cell lines) and IL-1B ($p<0.001$). IL-1R1 ($p<0.01$), CASP ($p<0.001$) and IL-1Ra ($p<0.01$) were further increased in tumor cells isolated from metastases in human bone compared with their corresponding mammary tumors, leading to further activation of IL-1β protein (FIG. **7**; FIG. **8**). These data suggest that IL-1β signalling may promote both initiation of metastasis from the primary site as well as development of breast cancer metastases in bone.

Tumor Derived IL-1β Promotes EMT and Breast Cancer Metastasis.

[0424] Expression levels of genes associated with tumor cell adhesion and epithelial to mesenchymal transition (EMT) were significantly altered in primary tumors that metastasised to bone compared with tumors that did not metastasise (FIG. **7**, panel c). IL-1β-overexpressing cells were generated (MDA-MB-231-IL-1B+, T47D-IL-1B+ and MCF7-IL-1B+) to investigate whether tumor-derived IL-1β is responsible for inducing EMT and metastasis to bone. All IL-1β+ cell lines demonstrated increased EMT exhibiting morphological changes from an epithelial to mesenchymal phenotype (FIG. **9**, panel a) as well as reduced expression of E-cadherin, and JUP (junction plakoglobin/gamma-catenin) and increased expression of N-Cadherin gene and protein (FIG. **9**, panel b). Wound closure ($p<0.0001$ in MDA-MB-231-IL-1β+(FIG. **9**, panel d); $p<0.001$ MCF7-IL-1β+ and T47D-IL-1β+) and migration and invasion through matrigel towards osteoblasts were increased in tumor cells with increased IL-1β signalling compared with their respective

controls (MDA-MB-231-IL-1β+(FIG. **9**, panel c) p<0.0001; MCF7-IL-1β+ and T47D-IL-1β+ p<0.001). Increased IL-1β production was seen in ER-positive and ER-negative breast cancer cells that spontaneously metastasized to human bone implants in vivo compared with non-metastatic breast cancer cells (FIG. **7**). The same link between IL-1β and metastasis was made in primary tumor samples from patients with stage II and III breast cancer enrolled in the AZURE study (Coleman et al., 2011) that experienced cancer relapsed over a 10 year time period. IL-1β expression in primary tumors from the AZURE patients correlated with both relapse in bone and relapse at any site indicating that presence of this cytokine is likely to play a role in metastasis in general. In agreement with this, genetic manipulation of breast cancer cells to artificially overexpress IL-1β increased the migration and invasion capacities of breast cancer cells in vitro (FIG. **9**).

Inhibition of IL-1β Signaling Reduces Spontaneous Metastasis to Human Bone.

[0425] As tumor derived IL-1β appeared to be promoting onset of metastasis through induction of EMT the effects of inhibiting IL-1β signaling with IL-1Ra (Anakinra) or a human anti-IL-1β-binding antibody (canakinumab) on spontaneous metastasis to human bone implants were investigated: Both IL-1Ra and canakinumab reduced metastasis to human bone: metastasis was detected in human bone implants in 7 out of 10 control mice, but only in 4 out of 10 mice treated with IL-1Ra and 1 out of 10 mice treated with canakinumab. Bone metastases from IL-1Ra and canakinumab treatment groups were also smaller than those detected in the control group (FIG. **10**, panel a). Numbers of cells detected in the circulation of mice treated with canakinumab or IL-1Ra were significantly lower than those detected in the placebo treated group: 3 and 3 tumor cells/ml were counted in whole blood from mice treated with canakinumab and anakinra, respectively, compared 108 tumor cells/ml counted in blood from placebo treated mice (FIG. **10**, panel b), suggesting that inhibition of IL-1 signalling prevents tumor cells from being shed from the primary site into the circulation. Therefore, inhibition of IL-1β signaling with the anti-IL-1β antibody canakinumab or inhibition of IL-1R1 reduced the number of breast cancer cells shed into the circulation and reduced metastases in human bone implants (FIG. **10**).

Tumor Derived IL-1B Promotes Bone Homing and Colonisation of Breast Cancer Cells.

[0426] Injection of breast cancer cells into the tail vein of mice usually results in lung metastasis due to the tumor cells becoming trapped in the lung capillaries. It was previously shown that breast cancer cells that preferentially home to the bone microenvironment following intra-venous injection express high levels of IL-1β, suggesting that this cytokine may be involved in tissue specific homing of breast cancer cells to bone. In the current study, intravenous injection of MDA-MB-231-IL-1β+ cells into BALB/c nude mice resulted in significantly increased number of animals developing bone metastasis (75%) compared with control cells (12%) (p<0.001) cells (FIG. **11**, panel a). MDA-MB-231-IL-1β+ tumors caused development of significantly larger osteolytic lesions in mouse bone compared with control cells (p=0.03; FIG. **11**, panel b) and there was a trend towards fewer lung metastases in mice injected with MDA-MB-231-IL-1β+ cells compared with control cells (p=0.16; FIG. **11**, panel c). These data suggest that endogenous IL-1β can promote tumor cell homing to the bone environment and development of metastases at this site.

Tumor Cell-Bone Cell Interactions Further Induce IL-1B and Promote Development of Overt Metastases.

[0427] Gene analysis data from a mouse model of human breast cancer metastasis to human bone implants suggested that the IL-1β pathway was further increased when breast cancer cells are growing in the bone environment compared with metastatic cells in the primary site or in the circulation (FIG. **7**, panel a). It was therefore investigated how IL-1β production changes when tumor cells come into contact with bone cells and how IL-1β alters the bone microenvironment to affect tumor growth (FIG. **12**). Culture of human breast cancer cells into pieces of whole human bone for 48h resulted in increased secretion of IL-1β into the medium (p<0.0001 for MDA-MB-231 and T47D cells; FIG. **12**, panel a). Co-culture with human HS5 bone marrow cells revealed the increased IL-1β concentrations originated from both the cancer cells (p<0.001) and bone marrow cells (p<0.001), with IL-1β from tumor cells increasing ~1000 fold and IL-1B from HS5 cells increasing ~100 fold following co-culture (FIG. **12**, panel b).

[0428] Exogenous IL-1β did not increase tumor cell proliferation, even in cells overexpressing IL-1R1. Instead, IL-1β stimulated proliferation of bone marrow cells, osteoblasts and blood vessels that in turn induced proliferation of tumor cells (FIG. **11**). It is therefore likely that arrival of tumor cells expressing high concentrations of IL-1β stimulate expansion of the metastatic niche components and contact between IL-1β expressing tumor cells and osteoblasts/blood vessels drive tumor colonization of bone. The effects of exogenous IL-1β as well as IL-1β from tumor cells on proliferation of tumor cells, osteoblasts, bone marrow cells and $CD34^+$ blood vessels were investigated: Co-culture of HS5 bone marrow or OB1 primary osteoblast cells with breast cancer cells caused increased proliferation of all cell types (P<0.001 for HS5, MDA-MB-231 or T47D, FIG. **12**, panel c) (P<0.001 for OB1, MDA-MB-231 or T47D, FIG. **12**, panel d). Direct contact between tumor cells, primary human bone samples, bone marrow cells or osteoblasts promoted release of IL-1β from both tumor and bone cells (FIG. **12**). Furthermore, administration of IL-1β increased proliferation of HS5 or OB1 cells but not breast cancer cells (FIG. **13**, panels a and b), suggesting that tumor cell-bone cell interactions promote production of IL-1β that can drive expansion of the niche and stimulate the formation of overt metastases.

[0429] IL-1β signalling was also found to have profound effects on the bone microvasculature: Preventing IL-1β signaling in bone by knocking out IL-1R1, pharmacological blockade of IL-1R with IL-Ra or reducing circulating concentrations of IL-1β by administering the anti-IL-1β binding antibody canakinumab reduced the average length of $CD34^+$ blood vessels in trabecular bone, where tumor colonisation takes place (p<0.01 for IL-1Ra and canakinumab treated mice) (FIG. **13**, panel c). These findings were confirmed by endomeucin staining which showed decreased numbers of blood vessels as well as blood vessel length in bone when IL-1β signaling was disrupted. ELISA analysis for endothelin 1 and VEGF showed reduced concentrations of both of

these endothelial cell markers in the bone marrow for IL-1R1$^{-/-}$ mice ($p<0.001$ endothelin 1; $p<0.001$ VEGF) and mice treated with IL-1R antagonist ($p<0.01$ endothlin 1; $p<0.01$ VEGF) or canakinumab ($p<0.01$ endothelin 1; $p<0.001$ VEGF) compared with control (FIG. **14**). These data suggest that tumor cell-bone cell associated increases in IL-1β and high levels of IL-1β in tumor cells may also promote angiogenesis, further stimulating metastases.

Tumor Derived IL-1β Predicts Future Breast Cancer Relapse in Bone and Other Organs in Patient Material

[0430] To establish the relevance of the findings in a clinical setting the correlation between IL-1β and its receptor IL-1R1 in patient samples was investigated. ~1300 primary tumor samples from patients with stage II/III breast cancer with no evidence of metastasis (from the AZURE study (Coleman et al., 2011)) were stained for IL-1R1 or the active (17 kD) form of IL-1β, and biopsies were scored separately for expression of these molecules in the tumor cells and the tumor associated stroma. Patients were followed up for 10 years following biopsy and correlation between IL-1β/IL-1R1 expression and distant recurrence or relapse in bone assessed using a multivariate Cox model. IL-1β in tumor cells strongly correlated with distant recurrence at any site ($p=0.0016$), recurrence only in bone ($p=0.017$) or recurrence in bone at any time ($p=0.0387$) (FIG. **15**). Patients who had IL-1β in their tumor cells and IL-1R1 in the tumor associated stroma were more likely to experience future relapse at a distant site ($p=0.042$) compared to patients who did not have IL-1β in their tumor cells, indicating that tumor derived IL-1β may not only promote metastasis directly but may also interact with IL-1R1 in the stroma to promote this process. Therefore, IL-1β is a novel biomarker that can be used to predict risk of breast cancer relapse.

Example 4

[0431] Simulation of Canakinumab PK Profile and hsCRP Profile for Lung Cancer Patients.

[0432] A model was generated to characterize the relationship between canakinumab pharmacokinetics (PK) and hsCRP based on data from the CANTOS study.

[0433] The following methods were used in this study: Model building was performed using the first-order conditional estimation with interaction method. The model described the logarithm of the time resolved hsCRP as:

$$y(t_{ij})=y_{0,i}+y_{eff}(t_{ij})$$

where $y_{0,i}$ is a steady state value and $y_{eff}(t_{ij})$ describes the effect of the treatment and depends on the systemic exposure. The treatment effect was described by an Emax-type model,

$$y_{eff}(t_{ij}) = E_{max,i}\frac{c(t_{ij})}{c(t_{ij})+IC50_i}$$

where $E_{max,i}$ is the maximal possible response at high exposure, and $IC50_i$ is the concentration at which half maximal response is obtained.

[0434] The individual parameters, $E_{max,i}$ and $y_{0,i}$ and the logarithm of $IC50_i$ were estimated as a sum of a typical value, covariate effects covpar*cov_i and normally distributed between subject variability. In the term for the covariate effect covpar refers to the covariate effect parameter being estimated and cov_i is the value of the covariate of subject i. Covariates to be included were selected based on inspection of the eta plots versus covariates. The residual error was described as a combination of proportional and additive term.

[0435] The logarithm of baseline hsCRP was included as covariate on all three parameters ($E_{max,i}$, $y_{0,i}$ and $IC50_i$). No other covariate was included into the model. All parameters were estimated with good precision. The effect of the logarithm of the baseline hsCRP on the steady state value was less than 1 (equal to 0.67). This indicates that the baseline hsCRP is an imperfect measure for the steady state value, and that the steady state value exposes regression to the mean relative to the baseline value. The effects of the logarithm of the baseline hsCRP on IC50 and Emax were both negative. Thus patients with high hsCRP at baseline are expected to have low IC50 and large maximal reductions. In general, model diagnostics confirmed that the model describes the available hsCRP data well.

[0436] The model was then used to simulate expected hsCRP response for a selection of different dosing regimens in a lung cancer patient population. Bootstrapping was applied to construct populations with intended inclusion/exclusion criteria that represent potential lung cancer patient populations. Three different lung cancer patient populations described by baseline hsCRP distribution alone were investigated: all CANTOS patients (scenario 1), confirmed lung cancer patients (scenario 2), and advanced lung cancer patients (scenario 3). The population parameters and inter-patient variability of the model were assumed to be the same for all three scenarios. The PK/PD relationship on hsCRP observed in the overall CANTOS population was assumed to be representative for lung cancer patients.

[0437] The estimator of interest was the probability of hsCRP at end of month 3 being below a cut point, which could be either 2 mg/L or 1.8 mg/L. 1.8 mg/L was the median of hsCRP level at end of month 3 in the CANTOS study. Baseline hsCRP>2 mg/L was one of the inclusion criteria, so it is worthy to explore if hsCRP level at end of month 3 went below 2 mg/L. A one-compartment model with first order absorption and elimination was established for CANTOS PK data. The model was expressed as ordinary differential equation and RxODE was used to simulate canakinumab concentration time course given individual PK parameters. The subcutaneous canakinumab dose regimens of interest were 300 mg Q12W, 200 mg Q3W, and 300 mg Q4W. Exposure metrics including Cmin, Cmax, AUCs over different selected time periods, and average concentration Cave at steady state were derived from simulated concentration time profiles.

[0438] The simulation in Scenario 1 was based on the below information:

Individual canakinumab exposure simulated using RxODE

[0439] PD parameters which are components of $y_{0,i}$, $E_{max,i}$, and $IC50_i$: typical values (THETA(3), THETA(5), THETA(6)), covpars (THETA(4), THETA(7), THETA(8)), and between subject variability (ETA(1), ETA(2), ETA(3))

[0440] Baseline hsCRP from all 10,059 CANTOS study patients (baseline hsCRP: mean 6.18 mg/L, standard error of the mean (SEM)=0.10 mg/L)

[0441] The prediction interval of the estimator of interest was produced by first randomly sampling 1000 THETA(3)-

(8)s from a normal distribution with fixed mean and standard deviation estimated from the population PK/PD model: and then for each set of THETA(3)-(8), bootstrapping 2000 PK exposure, PD parameters ETA(1)-(3), and baseline hsCRP from all CANTOS patients. The 2.5%, 50%, and 97.5% percentile of 1000 estimates were reported as point estimator as well as 95% prediction interval.

[0442] The simulation in Scenario 2 was based on the below information:

[0443] Individual canakinumab PK exposure simulated using RxODE

[0444] PD parameters THETA(3)-(8) and ETA(1)-(3)

[0445] Baseline hsCRP from 116 CANTOS patients with confirmed lung cancer (baseline hsCRP: mean=9.75 mg/L, SEM=1.14 mg/L)

[0446] The prediction interval of the estimator of interest was produced by first randomly sampling 1000 THETA(3)-(8)s from a normal distribution with fixed mean and standard deviation estimated from the population PKPD model; and then for each set of THETA(3)-(8), bootstrapping 2000 PK exposure, PD parameters ETA(1)-(3) from all CANTOS patients, and bootstrapping 2000 baseline hsCRP from the 116 CANTOS patients with confirmed lung cancer. The 2.5%, 50%, and 97.5% percentile of 1000 estimates were reported as point estimator as well as 95% prediction interval.

[0447] In Scenario 3, the point estimator and 95% prediction interval were obtained in a similar manner as for scenario 2. The only difference was bootstrapping 2000 baseline hsCRP values from advanced lung cancer population. There is no individual baseline hsCRP data published in an advanced lung cancer population. An available population level estimate in advanced lung cancer is a mean of baseline hsCRP of 23.94 mg/L with SEM 1.93 mg/L [Vaguliene 2011]. Using this estimate, the advanced lung cancer population was derived from the 116 CANTOS patients with confirmed lung cancer using an additive constant to adjust the mean value to 23.94 mg/L.

[0448] In line with the model, the simulated canakinumab PK was linear. The median and 95% prediction interval of concentration time profiles are plotted in natural logarithm scale over 6 months is shown in FIG. **16**, panel a.

[0449] The median and 95% prediction intervals of 1000 estimates of proportion of subjects with month 3 hsCRP response under the cut point of 1.8 mg/L and 2 mg/L mhsCRP are reported in FIG. **16**, panels b and c. Judging from the simulation data, 200 mg Q3W and 300 mg Q4W perform similarly and better than 300 mg Q12W (top dosing regimen in CANTOS) in terms of decreasing hsCRP at month 3. Going from scenario 1 to scenario 3 towards more severe lung cancer patients, higher baseline hsCRP levels are assumed, and result in smaller probabilities of month 3 hsCRP being below the cut point. FIG. **16**, panel d shows how the median hsCRP concentration changes over time for three different doses and FIG. **16**, panel e shows the percent reduction from baseline hsCRP after a single dose.

Example 5A

PDR001 Plus Canakinumab Treatment Increases Effector Neutrophils in Colorectal Tumors.

[0450] RNA sequencing was used to gain insights on the mechanism of action of canakinumab (ACZ885) in cancer. The CPDR001X2102 and CPDR001X2103 clinical trials evaluate the safety, tolerability and pharmacodynamics of spartalizumab (PDR001) in combination with additional therapies. For each patient, a tumor biopsy was obtained prior to treatment, as well as cycle 3 of treatment. In brief, samples were processed by RNA extraction, ribosomal RNA depletion, library construction and sequencing. Sequence reads were aligned by STAR to the hg19 reference genome and Refseq reference transcriptome, gene-level counts were compiled by HTSeq, and sample-level normalization using the trimmed mean of M-values was performed by edgeR

[0451] FIG. **17** shows 21 genes that were increased, on average, in colorectal tumors treated with PDR001+canakinumab (ACZ885), but not in colorectal tumors treated with PDR001+everolimus (RAD001). Treatment with PDR001+canakinumab increased the RNA levels of IL1B, as well as its receptor, IL1R2. This observation suggests an on-target compensatory feedback by tumors to increase IL1B RNA levels in response to IL-1β protein blockade.

[0452] Notably, several neutrophil-specific genes were increased on PDR001+ canakinumab, including FCGR3B, CXCR2, FFAR2, OSM, and G0S2 (indicated by boxes in FIG. **17**). The FCGR3B gene is a neutrophil-specific isoform of the CD16 protein. The protein encoded by FCGR3B plays a pivotal role in the secretion of reactive oxygen species in response to immune complexes, consistent with a function of effector neutrophils (Fossati G 2002 Arthritis Rheum 46: 1351). Chemokines that bind to CXCR2 mobilize neutrophils out of the bone marrow and into peripheral sites. In addition, increased CCL3 RNA was observed on treatment with PDR001+ canakinumab. CCL3 is a chemoattractant for neutrophils (Reichel C A 2012 Blood 120: 880).

[0453] In summary, this contribution of components analysis using RNA-seq data demonstrates that PDR001+canakinumab treatment increases effector neutrophils in colorectal tumors, and that this increase was not observed with PDR001+everolimus treatment.

Example 5B

[0454] Efficacy of Canakinumab (ACZ885) in Combination with Spartalizumab (PDR001) in the Treatment of Cancer.

[0455] Patient 5002-004 is a 56 year old man with initially Stage IIC, microsatellite-stable, moderately differentiated adenocarcinoma of the ascending colon (MSS-CRC), diagnosed in June, 2012 and treated with prior regimens.

[0456] Prior treatment regimens included:

1. Folinic acid/5-fluoruracil/oxaliplatin in the adjuvant setting
2. Chemoradiation with capecitabine (metastatic setting)
3. 5-fluorouracil/bevacizumab/folinic acid/irinotecan
4. trifluridine and tipiracil
5. Irinotecan

[0457] 6. Oxaliplatin/5-fluorouracil
7. 5-fluorouracil/bevacizumab/leucovorin
8. 5-fluorouracil

[0458] At study entry the patient had extensive metastatic disease including multiple hepatic and bilateral lung metastases, and disease in paraesophageal lymph nodes, retroperitoneum and peritoneum.

[0459] The patient was treated with PDR001 400 mg every four weeks (Q4W) plus 100 mg every eight weeks (Q8W) ACZ885. The patient had stable disease for 6 months

of therapy, then with substantial disease reduction and confirmed RECIST partial response to treatment at 10 months. The patient has subsequently developed progressive disease and the dose was increased to 300 mg and then to 600 mg.

Example 6

Calculations for Selecting the Dose for Gevokizumab for Cancer Patients.

[0460] Dose selection for gevokizumab in the treatment of cancer having at least partial inflammatory basis is based on the clinical effective dosings reveals by the CANTOS trial in combination with the available PK data of gevokizumab, taking into the consideration that Gevokizumab (IC50 of ~2-5 pM) shows a ~10 times higher in vitro potency compared to canakinumab (IC50 of ~42±3.4 pM). The gevokizumab top dose of 0.3 mg/kg (~20 mg) Q4W showed reduction of hsCRP in patients that is non-saturating (see FIG. **18**, panel a).

[0461] Next, a pharmacometric model was used to explore the hsCRP exposure-response relationship, and to extrapolate the clinical data to higher ranges. As clinical data show a linear correlation between the hsCRP concentration and the concentration of gevokizumab (both in log-space), a linear model was used. The results are shown in FIG. **18**, panel b. Based on that simulation, a gevokizumab concentration between 10000 ng/mL and 25000 ng/mL is optimal because hsCRP is greatly reduced in this range, and there is only a diminishing return with gevokizumab concentrations above 15000 ng/mL.

[0462] Clinical data showed that gevokizumab pharmacokinetics follow a linear two-compartment model with first order absorption after a subcutaneous administration. Bioavailability of gevokizumab is about 56%0/when administered subcutaneously. Simulation of multiple-dose gevokizumab was carried out for 100 mg every four weeks (see FIG. **18**, panel c) and 200 mg every four weeks (see FIG. **18**, panel d). The simulations showed that the trough concentration of 100 mg gevokizumab given every four weeks is about 10700 ng/mL. The half-life of gevokizumab is about 35 days. The trough concentration of 200 mg gevokizumab given every four weeks is about 21500 ng/mL.

Example 7

Preclinical Data on the Effects of Anti-IL-1Beta Treatment.

[0463] Canankinumab, an anti-IL-1beta human IgG1 antibody, cannot directly be evaluated in mouse models of cancer due to the fact that it does not cross-react with mouse IL-1beta. A mouse surrogate anti-IL-1beta antibody has been developed and is being used to evaluate the effects of blocking IL-1beta in mouse models of cancer. This isotype of the surrogate antibody is IgG2a, which is closely related to human IgG.

[0464] In the MC38 mouse model of colon cancer, modulation of tumor infiltrating lymphocytes (TILs) can be seen after one dose of the anti IL-1beta antibody (FIG. **19**, panels a, b, and c). MC38 tumors were subcutaneously implanted in the flank of C57BL/6 mice and when the tumors were between 100-150 mm^3, the mice were treated with one dose of either an isotype antibody or the anti IL-1 beta antibody. Tumors were then harvested five days after the dose and processed to obtain a single cell suspension of immune cells. The cells were then ex vivo stained and analyzed via flow cytometry. Following a single dose of an IL-1beta blocking antibody, there is an increase in $CD4^+$ T cells infiltrating the tumor and also a slight increase in $CD8^+$ T cells (FIG. **19**, panel a). The CD8+ T cell increase is slight but may allude to a more active immune response in the tumor microenvironment, which could potentially be enhanced with combination therapies. The $CD4^+$ T cells were further subdivided into $FoxP3^+$ regulatory T cells (Tregs), and this subset decreases following blockade of IL-1beta (FIG. **19**, panel b). Among the myeloid cell populations, blockade of IL-1beta results in a decrease in neutrophils and the M2 subset of macrophages, TAM2 (FIG. **19**, panel c). Both neutrophils and M2 macrophages can be suppressive to other immune cells, such as activated T cells (Pillay et al, 2013; Hao et al, 2013; Oishi et al 2016). Taken together, the decrease in Tregs, neutrophils, and M2 macrophages in the MC38 tumor microenvironment following IL-1beta blockade argues that the tumor microenvironment is becoming less immune suppressive.

[0465] In the LL2 mouse model of lung cancer, a similar trend towards a less suppressive immune microenvironment can be seen after one dose of an anti-IL-1beta antibody (FIG. **19**, panels d and e). LL2 tumors were subcutaneously implanted in the flank of C57BL/6 mice and when the tumors were between 100-150 mm^3, the mice were treated with one dose of either an isotype antibody or the anti IL-1beta antibody. Tumors were then harvested five days after the dose and processed to obtain a single cell suspension of immune cells. The cells were then ex vivo stained and analyzed via flow cytometry. There is a decrease in the Treg populations as evaluated by the expression of FoxP3 and Helios (FIG. **19**, panel d). FoxP3 and Helios are both used as markers of regulatory T cells, while they may define different subsets of Tregs (Thornton et al, 2016). Similar to the MC38 model, there is a decrease in both neutrophils and M2 macrophages (TAM2) following IL-1beta blockade (FIG. **19**, panel e). Again, the decrease in Tregs, neutrophils, and M2 macrophages in the LL2 model following IL-1beta blockade argues that the tumor microenvironment is becoming less immune suppressive.

[0466] Mouse models do not always correlate to the same type of cancer in humans due to genetic differences in the origins of the cancer in mice versus humans. However, when examining the infiltrating immune cells, the type of cancer is not always important, as the immune cells are more relevant. In this case, as two different mouse models show a similar decrease in the suppressive microenvironment of the tumor, blocking IL-1 beta seems to lead to a less suppressive tumor microenvironment.

TABLE 1

Baseline clinical characteristics of participants in CANTOS among those who did and did not develop incident cancers during follow-up.

	No Incident Cancers		Incident Non-Lung Cancers		Incident Lung Cancers	
	Placebo (N = 3113)	Canakinumab (N = 6286)	Placebo (N = 179)	Canakinumab (N = 377)	Placebo (N = 61)	Canakinumab (N = 68)
Age (yr)	61.0	61.0	67.0	66.0	66.0	64.0
Female sex (%)	26.3	25.8	22.3	22.5	14.8	26.5
Smoking status (%)						
Current smoking	22.3	23.6	25.7	24.7	45.9	42.6
Past smoking	48.0	46.5	55.3	48.8	50.8	54.4
Never smoker	29.7	29.9	19.0	26.5	3.3	2.9
Body mass index (kg/m^2)	29.8	29.8	29.0	30.1	28.3	29.7
Waist circumference (cm)	104	104	103	106	106	110
Alcohol use (%, >1/day)	4.0	3.9	5.6	4.5	3.3	2.9
Hypertension (%)	78.8	79.6	84.9	84.9	78.7	73.5
Diabetes (%)	39.7	39.9	40.8	44.3	45.9	38.2
Daily Exercise (%)	17.5	16.9	19.6	18.1	11.5	10.3
hsCRP (mg/L)	4.1	4.2	4.3	4.4	6.8	6.0
Interleukin-6 (ng/L)	2.6	2.6	3.0	2.6	3.4	3.1
Total cholesterol (mg/dL)	161	160	152	153	159	160
LDL cholesterol (mg/dL)	83	83	76	75	77	80
HDL cholesterol (mg/dL)	44	44	46	45	45	42
Triglycerides (mg/dL)	139	140	127	130	140	135
eGFR ($mL/min/1.73\ m^2$)	79	79	75	74	72	78

*Shown are median within group levels of characteristics for continuous variables, and percentages for dichotomous variables

TABLE 2

Incidence rates (per 100 person years) and hazard ratios for all incident cancers, lung cancers, and non-lung cancers in CANTOS.

		Canakinumab Dose (SC q 3 months)				P-value for trend
Clinical Outcome	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	across doses
Any Cancer (all)						
Incident rate, (N)	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31
Hazard ratio	1.00	0.99	0.90	0.91	0.93	
95% CI	(referent)	0.80-1.22	0.73-1.11	0.74-1.12	0.79-1.09	
P	(referent)	0.91	0.31	0.38	0.38	
Any Cancer (fatal)						
Incidence rate, (N)	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	0.0007
Hazard ratio	1.00	0.86	0.78	0.49	0.71	
95% CI	(referent)	0.59-1.24	0.54-1.13	0.31-0.75	0.53-0.94	
P	(referent)	0.42	0.19	0.0009	0.016	
Lung Cancer (all)						
Incidence rate, (N)	0.49 (61)	0.35 (28)	0.30 (26)	0.16 (14)	0.27 (68)	<0.0001
Hazard ratio	1.00	0.74	0.61	0.33	0.55	
95% CI	(referent)	0.47-1.17	0.39-0.97	0.18-0.59	0.39-0.78	
P	(referent)	0.20	0.034	<0.0001	0.0007	

TABLE 2-continued

Incidence rates (per 100 person years) and hazard ratios for all incident cancers, lung cancers, and non-lung cancers in CANTOS.

Clinical Outcome	Placebo (N = 3344)	Canakinumab Dose (SC q 3 months) 50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses
Lung Cancer (fatal)						
Incidence rate, (N)	0.30 (38)	0.20 (16)	0.19 (17)	0.07 (6)	0.15 (39)	0.0002
Hazard ratio	1.00	0.67	0.64	0.23	0.51	
95% CI	(referent)	0.37-1.20	0.36-1.14	0.10-0.54	0.33-0.80	
P	(referent)	0.18	0.13	0.0002	0.0026	
Non-Lung Cancer (all)						
Incidence rate, (N)	1.46 (179)	1.55 (121)	1.44 (122)	1.60 (134)	1.53 (377)	0.54
Hazard ratio	1.00	1.08	0.99	1.10	1.05	
95% CI	(referent)	0.85-1.36	0.78-1.24	0.88-1.37	0.88-1.26	
P	(referent)	0.54	0.91	0.42	0.58	
Non-Lung Cancer (fatal)						
Incidence rate, (N)	0.39 (49)	0.38 (30)	0.34 (30)	0.24 (21)	0.32 (81)	0.06
Hazard ratio	1.00	0.96	0.88	0.63	0.82	
95% CI	(referent)	0.61-1.51	0.56-1.39	0.38-1.04	0.58-1.17	
P	(referent)	0.86	0.60	0.07	0.28	

TABLE 3

Effects of canakinumab as compared to placebo on platelets, leucocytes, neutrophils, and erythrocytes reported as adverse events and after 12 months of treatment with study drug during CANTOS.

Adverse Event	Placebo (N = 3344)	Canakinumab Dose (SC q 3 months) 50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Thrombocytopenia (AE reports)+ Platelets (at 12 months)*	53 (0.43)	44 (0.56)	46 (0.54)	60 (0.71)	150 (0.60)	0.010	0.029
Normal N (%)	2731 (91.1)	1741 (88.9)	1777 (87.5)	1698 (84.0)	5216 (86.8)	<0.0001	<0.0001
Grade 1 (75.000-<LLN)	259 (8.6)	214 (10.9)	252 (12.4)	316 (15.6)	782 (13.0)		
Grade 2 (50,000-<75,000)	6 (0.20)	3 (0.15)	1 (0.05)	6 (0.30)	10 (0.17)		
Grade 3 (25,000-<50,000)	1 (0.03)	0 (0.00)	2 (0.10)	2 (0.10)	4 (0.07)		
Grade 4 (<25,000)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)		
Leukopenia (AE reports)+ Leucocytes (at 12 months)*	30 (0.24)	24 (0.30)	32 (0.37)	44 (0.52)	100 (0.40)	0.001	0.013
High (>15,000)	11 (0.37)	9 (0.46)	9 (0.44)	2 (0.10)	20 (0.33)	0.09	0.56
Normal (3000-<15000)	2980 (99.3)	1944 (99.2)	2016 (99.0)	2018 (99.5)	5978 (99.2)		
Low (<3000)	9 (0.30)	7 (0.36)	11 (0.54)	9 (0.44)	27 (0.45)		
Neutropenia (AE reports)	7 (0.06)	4 (0.05)	6 (0.07)	15 (0.18)	25 (0.10)	0.003	0.17

TABLE 3-continued

Effects of canakinumab as compared to placebo on platelets, leucocytes, neutrophils, and erythrocytes reported as adverse events and after 12 months of treatment with study drug during CANTOS.

	Canakinumab Dose (SC q 3 months)						
Adverse Event	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Neutrophils (at 12 months)*							
Normal N (%)	2954 (99.4)	1917 (99.4)	1991 (99.1)	1983 (99.2)	5891 (99.2)	0.33	0.72
Grade 1 (1500-<LLN)	5 (0.17)	4 (0.21)	4 (0.20)	6 (0.30)	14 (0.24)		
Grade 2 (1000-<1500)	10 (0.34)	6 (0.31)	12 (0.60)	10 (0.50)	28 (0.47)		
Grade 3 (500-<1000)	3 (0.10)	2 (0.10)	2 (0.10)	1 (0.05)	5 (0.08)		
Grade 4 (<500)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)		
Anemia (AE reports)	168 (1.37)	63 (0.80)	102 (1.21)	110 (1.31)	275 (1.11)	0.57	0.033
Erythrocytes (at 12 months)**							
High (>6.8)	2 (0.07)	1 (0.05)	0 (0.00)	3 (0.15)	4 (0.07)	0.31	0.62
Normal (3.3-6.8)	2993 (99.7)	1954 (99.7)	2031 (99.8)	2017 (99.4)	6002 (99.6)		
Low (<3.3)	6 (0.20)	5 (0.26)	5 (0.25)	9 (0.44)	19 (0.32)		

+Standardized MedDRA query

*values per cubic mm

**$\times 10^{12}$

TABLE 4

Incidence rates (per 100-person years), number (N) of serious adverse events, and selected on-treatment safety laboratory data (%; N), stratified by study group.

	Canakinumab Dose (SC q 3 months)						
Adverse Event or Laboratory Parameter	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Any SAE	11.8 (1192)	11.4 (740)	11.6 (803)	12.3 (833)	11.7 (2376)	0.41	0.86
Any SAE infection	2.83 (339)	2.97 (225)	3.12 (257)	3.25 (265)	3.11 (747)	0.09	0.14
Cellulitis	0.24 (30)	0.23 (18)	0.37 (32)	0.41 (35)	0.34 (85)	0.018	0.10
Pneumonia	0.89 (111)	0.90 (71)	0.92 (79)	0.97 (83)	0.93 (233)	0.54	0.69
Urinary tract	0.22 (27)	0.18 (14)	0.24 (21)	0.20 (17)	0.21 (52)	0.84	0.87
Opportunistic infections++	0.18 (23)	0.16 (13)	0.15 (13)	0.20 (17)	0.17 (43)	0.97	0.78
Pseudomembranous Colitis+	0.03 (4)	0.11 (9)	0.05 (4)	0.12 (10)	0.09 (23)	0.10	0.038
Fatal infection/sepsis	0.18 (23)	0.31 (25)	0.28 (24)	0.34 (29)	0.31 (78)	0.09	0.023
Other adverse events							
Injection site reaction++	0.23 (29)	0.27 (21)	0.28 (24)	0.30 (26)	0.28 (71)	0.49	0.36
Arthritis+	3.20 (373)	2.07 (158)	2.12 (176)	2.43 (198)	2.21 (532)	0.005	<0.001
Osteoarthritis	1.62 (196)	1.15 (90)	1.10 (93)	1.25 (105)	1.17 (288)	0.038	0.001
Gout	0.80 (98)	0.42 (33)	0.31 (27)	0.37 (32)	0.37 (92)	<0.001	<0.001
Drug induced liver injury (SAE)++	0.18 (23)	0.15 (12)	0.13 (11)	0.05 (4)	0.11 (27)	0.004	0.054
Any Hemorrhage+	3.95 (455)	3.26 (244)	4.09 (323)	3.75 (296)	3.71 (863)	0.94	0.31

TABLE 4-continued

Incidence rates (per 100-person years), number (N) of serious adverse events, and selected on-treatment safety laboratory data (%; N), stratified by study group.

Adverse Event or Laboratory Parameter	Canakinumab Dose (SC q 3 months)						
	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Hepatic							
ALT > 3x normal %, (N)	1.4 (46)	1.9 (42)	1.9 (44)	2.0 (45)	2.0 (131)	0.19	0.059
AST > 3x normal %, (N)	1.1 (36)	1.5 (32)	1.5 (35)	1.5 (34)	1.5 (101)	0.29	0.11
ALP > 3x normal %, (N)	0.4 (15)	0.5 (11)	0.4 (10)	0.5 (12)	0.5 (33)	0.67	0.81
Bilirubin > 2x normal %, (N)	0.8 (26)	1.0 (21)	0.7 (15)	0.7 (15)	0.8 (51)	0.34	0.82

+Standardized MedDRA query

++Sponsor categorization of adverse events of special interest

TABLE 5

Proportion of Month 3 hsCRP < cut point (Median and 95% prediction interval).

Scenario[##]/ Cut point (mg/L)	300 mg Q12W	200 mg Q3W	300 mg Q4W
1/2.0	0.6615 (0.6380, 0.6840)	0.7715 (0.7480, 0.7940)	0.7715 (0.7480, 0.7940)
1/1.8	0.5860 (0.5615, 0.6105)	0.7110 (0.6860, 0.7355)	0.7110 (0.6865, 0.7355)
2/2.0	0.5355 (0.5075, 0.5610)	0.6450 (0.6135, 0.6765)	0.6450 (0.6135, 0.6770)
2/1.8	0.4610 (0.4345, 0.4860)	0.5760 (0.5440, 0.6070)	0.5760 (0.5440, 0.6065)

TABLE 5-continued

Proportion of Month 3 hsCRP < cut point (Median and 95% prediction interval).

Scenario[##]/ Cut point (mg/L)	300 mg Q12W	200 mg Q3W	300 mg Q4W
3/2.0	0.1560 (0.1265, 0.1890)	0.2110 (0.1674, 0.2595)	0.2110 (0.1674, 0.2595)
3/1.8	0.1095 (0.0850, 0.1340)	0.1495 (0.1150, 0.1890)	0.1495 (0.1150, 0.1885)

[##]From Scenario 1 to Scenario 3, the severity of lung cancer increased. The means of baseline hsCRP are 6.18 mg/L, 9.75 mg/L, and 23.94 mg/L, respectively.

TABLE S1

Baseline clinical characteristics of CANTOS participants by treatment status.

Characteristic	Canakinumab Dose (SC q 3 months)				
	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)
Mean age (yr)	61.1	61.1	61.2	61.1	61.1
Female sex (%)	25.9	24.9	25.2	26.8	25.6
Current smoking (%)	22.9	24.5	23.4	23.7	23.8
Body mass index (kg/m^2)	29.7	29.9	29.8	29.8	29.9
Hypertension (%)	79.1	80.7	79.4	79.5	79.9
Diabetes (%)	39.9	39.4	41.8	39.2	40.1
Qualifying myocardial infarction (%)					
STEMI	54.0	56.7	53.9	53.6	54.7
Non-STEMI	33.9	32.7	34.2	33.6	33.5
Unknown/missing	12.1	10.6	11.8	12.8	11.7
History of PCI (%)	65.6	67.0	68.1	66.7	67.3
History of CABG (%)	14.0	13.9	14.2	14.0	14.0
History of congestive heart failure (%)	21.6	20.8	20.9	23.1	21.6
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5	93.3
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6	79.3
Anti-ischemia agents* (%)	92.1	91.0	91.2	91.1	91.0
hsCRP (mg/L)	4.1	4.25	4.25	4.15	4.2
Il-6 (ng/L)	2.61	2.53	2.56	2.59	2.56
Total cholesterol (mg/dL)	160.5	159.0	159.0	161.0	159.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5	82.0
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0	43.7

TABLE S1-continued

Baseline clinical characteristics of CANTOS participants by treatment status.

Characteristic	Canakinumab Dose (SC q 3 months)				
	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)
Triglycerides (mg/dL)	139.0	139.9	139.1	138.2	139.1
eGFR (mL/min/1.73 m^2)	79.0	79.0	79.0	78.0	78.5
Loss to follow-up N, (%)	9 (0.27)	9 (0.41)	5 (0.22)	4 (0.18)	18 (0.27)

STEMI = ST elevation myocardial infarction;
PCI = percutaneous coronary intervention;
CABG = coronary bypass graft surgery;
hsCRP = high sensitivity C-reactive protein;
HDL = high density lipoprotein cholesterol;
LDL = low density lipoprotein cholesterol;
eGFR = estimated glomerular filtration rate
*Beta-blocking agents, nitrates, or calcium channel blocking agents
Median values are presented for all measured plasma variables and body mass index

TABLE S2

Incidence rates (Per 100 person years) and hazard ratios for lung cancers among current and past smokers.

		Canakinumab Dose (SC q 3 months)				P-value for trend
	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	across doses
Lung Cancer, Current Smokers						
Incident rate, (N)	0.97 (28)	0.46 (9)	0.75 (15)	0.25 (5)	0.49 (29)	0.005
Hazard ratio	1.00	0.49	0.76	0.25	0.50	
95% CI	(referent)	0.23-1.05	0.40-1.42	0.10-0.65	0.30-0.84	
P	(referent)	0.06	0.38	0.002	0.007	
Lung Cancer, Past Smokers						
Incidence rate, (N)	0.51 (31)	0.48 (18)	0.25 (10)	0.23 (9)	0.31 (37)	0.006
Hazard ratio	1.00	0.95	0.48	0.44	0.61	
95% CI	(referent)	0.53-1.71	0.24-0.99	0.21-0.92	0.38-0.99	
P	(referent)	0.87	0.041	0.025	0.043	

TABLE S3

Incidence rates per 100 person years and (number) for lung cancer types and other site-specific non-lung cancers in CANTOS.

Cancer Site or Type	Canakinumab Dose (SC q 3 months)						
	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Lung Cancers							
Adenocarcinoma or poorly differentiated large cell carcinoma or unspecified	0.41 (52)	0.33 (26)	0.27 (23)	0.12 (10)	0.23 (59)	<0.001	0.002
Squamous cell lung carcinoma	0.03 (4)	0.01 (1)	0.02 (2)	0.03 (3)	0.02 (6)	0.74	0.65
Small cell lung cancer	0.04 (5)	0.01 (1)	0.01 (1)	0.01 (1)	0.01 (3)	NA	NA
Pleural cancer	0.01 (1)	0	0	0	0	NA	NA
Other Cancer Sites							
Skin							
Basal cell carcinoma	0.18 (23)	0.28 (22)	0.29 (25)	0.21 (18)	0.26 (65)	0.80	0.16
Squamous cell skin cancer	0.16 (20)	0.10 (8)	0.15 (13)	0.27 (23)	0.17 (44)	0.036	0.74

TABLE S3-continued

Incidence rates per 100 person years and (number) for lung cancer types and other site-specific non-lung cancers in CANTOS.

	Canakinumab Dose (SC q 3 months)						
Cancer Site or Type	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	P-value for trend across doses	P-value for combined dose groups
Melanoma	0.02 (3)	0.08 (6)	0.06 (5)	0.06 (5)	0.06 (16)	0.44	0.11
Other	0.06 (8)	0	0.06 (5)	0.02 (2)	0.03 (7)	0.41	0.10
Gastrointenstinal							
Oral cavity/tongue	0.02 (3)	0.03 (2)	0.05 (4)	0.02 (2)	0.03 (8)	0.99	0.69
Esophageal	0.06 (8)	0.08 (6)	0.03 (3)	0.08 (7)	0.06 (16)	0.80	1.00
Gastric	0.08 (10)	0.04 (3)	0.02 (2)	0.06 (5)	0.04 (10)	0.54	0.11
Colorectal	0.16 (20)	0.25 (20)	0.19 (16)	0.21 (18)	0.21 (54)	0.66	0.26
Biliary	0.01 (1)	0.03 (2)	0.03 (3)	0	0.02 (5)	NA	NA
Appendiceal	0.01 (1)	0	0	0.01 (1)	0.00 (1)	NA	NA
Pancreatic	0.06 (8)	0.04 (3)	0.06 (5)	0.06 (5)	0.05 (13)	0.95	0.64
Hematopoetic							
Lymphoma	0.06 (7)	0.04 (3)	0.05 (4)	0.07 (6)	0.05 (13)	0.57	0.87
Leukemia	0.01 (1)	0.01 (1)	0.02 (2)	0.01 (1)	0.02 (4)	NA	NA
Multiple myeloma	0.02 (2)	0	0	0.02 (2)	0.01 (2)	NA	NA
Endocrine							
Thyroid	0.03 (4)	0.01 (1)	0.02 (2)	0.01 (1)	0.02 (4)	NA	NA
Adrenal	0.02 (2)	0	0.01 (1)	0.01 (1)	0.01 (2)	NA	NA
Genitourinary							
Bladder	0.06 (8)	0.10 (8)	0.08 (7)	0.13 (11)	0.10 (26)	0.21	0.23
Prostate	0.15 (19)	0.19 (15)	0.16 (14)	0.17 (15)	0.17 (44)	0.85	0.60
Testicular	0	0	0.01 (1)	0	0.00 (1)	NA	NA
Ovarian	0	0	0.01 (1)	0	0.00 (1)	NA	NA
Endometrial/Uterine	0.01 (1)	0.03 (2)	0	0.03 (3)	0.02 (5)	NA	NA
Cervical	0.01 (1)	0	0.01 (1)	0	0.00 (1)	NA	NA
Breast	0.06 (8)	0.09 (7)	0.05 (4)	0.06 (5)	0.06 (16)	0.63	0.99
Kidney	0.06 (8)	0.13 (10)	0.07 (6)	0.07 (6)	0.09 (22)	0.77	0.44
Liver	0.07 (9)	0.04 (3)	0.06 (5)	0.03 (3)	0.04 (11)	0.38	0.26
Central Nervous System	0.01 (1)	0.04 (3)	0.05 (4)	0.03 (3)	0.04 (10)	0.33	0.09
Sarcoma/Bone	0.03 (4)	0.01 (1)	0	0.01 (1)	0.01 (2)	NA	NA
Other	0.09 (11)	0.08 (6)	0.06 (5)	0.02 (2)	0.05 (13)	0.047	0.19

NA - tests for significance not performed if event number <10.

TABLE S4

Sensitivity analysis of incidence rates (per 100 person years) and hazard ratios based upon all reported cancers in CANTOS rather than on adjudicated cancers.

		Canakinumab Dose (SC q 3 months)				P-value for trend
Clinical Outcome	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	across doses
Any Reported Cancer (all)						
Incident rate, (N)	1.93 (237)	1.88 (146)	1.76 (148)	1.78 (149)	1.80 (443)	0.38
Hazard ratio	1.00	0.98	0.91	0.92	0.93	
95% CI	(referent)	0.79-1.20	0.74-1.11	0.75-1.13	0.80-1.09	
P	(referent)	0.82	0.35	0.43	0.39	
Any Reported Cancer (fatal)						
Incidence rate, (N)	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	0.0007
Hazard ratio	1.00	0.86	0.78	0.49	0.71	
95% CI	(referent)	0.59-1.24	0.54-1.13	0.31-0.75	0.53-0.94	
P	(referent)	0.42	0.19	0.0009	0.016	
Reported Lung Cancer (all)						
Incidence rate, (N)	0.50 (62)	0.35 (28)	0.31 (27)	0.20 (17)	0.29 (72)	0.0003
Hazard ratio	1.00	0.73	0.62	0.39	0.58	

TABLE S4-continued

Sensitivity analysis of incidence rates (per 100 person years) and hazard ratios based upon all reported cancers in CANTOS rather than on adjudicated cancers.

		Canakinumab Dose (SC q 3 months)				P-value for trend
Clinical Outcome	Placebo (N = 3344)	50 mg (N = 2170)	150 mg (N = 2284)	300 mg (N = 2263)	All Doses (N = 6717)	across doses
95% CI	(referent)	0.47-1.15	0.40-0.98	0.23-0.67	0.41-0.81	
P	(referent)	0.17	0.040	0.0004	0.0013	
Reported Lung Cancer (fatal)						
Incidence rate, (N)	0.30 (38)	0.20 (16)	0.19 (17)	0.07 (6)	0.15 (39)	0.0002
Hazard ratio	1.00	0.67	0.64	0.23	0.51	
95% CI	(referent)	0.37-1.20	0.36-1.14	0.10-0.54	0.33-0.80	
P	(referent)	0.18	0.13	0.0002	0.0026	
Reported Non-Lung Cancer (all)						
Incidence rate, (N)	1.54 (189)	1.62 (126)	1.53 (129)	1.66 (139)	1.60 (394)	0.60
Hazard ratio	1.00	1.06	0.99	1.08	1.04	
95% CI	(referent)	0.85-1.33	0.79-1.24	0.87-1.34	0.88-1.24	
P	(referent)	0.62	0.93	0.50	0.65	
Reported Non-Lung Cancer (fatal)						
Incidence rate, (N)	0.41 (52)	0.40 (32)	0.37 (32)	0.27 (23)	0.34 (87)	0.07
Hazard ratio	1.00	0.97	0.89	0.64	0.83	
95% CI	(referent)	0.63-1.51	0.57-1.38	0.39-1.05	0.59-1.17	
P	(referent)	0.91	0.59	0.08	0.29	

SPECIFIC EMBODIMENTS

[0467] While various specific embodiments have been illustrated and described, it will be appreciated that various changes can be made without departing from the spirit and scope of the disclosure(s). The present disclosure is exemplified by the numbered embodiments set forth below.

[0468] 1. An IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment and/or prevention of a cancer having at least partial inflammatory basis.

[0469] 2. An IL-1β binding antibody or a functional fragment thereof for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis.

[0470] 3. The embodiment of claim **1** or **2**, wherein said cancer having at least partial inflammatory basis is selected from the list consisting of lung cancer, especially NSCLC, colorectal cancer (CRC), melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma, acute myeloblastic leukemia (AML), and biliary tract cancer.

[0471] 4. The first or second embodiment above, wherein said cancer having at least partial inflammatory basis is selected from the list consisting of lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0472] 5. The first or second embodiment above, wherein said cancer having at least partial inflammatory basis is colorectal cancer (CRC).

[0473] 6. The first or second embodiment above, wherein said cancer having at least partial inflammatory basis is renal cell carcinoma (RCC).

[0474] 7. The first or second embodiment above, wherein said cancer having at least partial inflammatory basis is breast cancer.

[0475] 8. The first or second embodiment above, wherein said cancer having at least partial inflammatory basis is lung cancer, preferably non-small cell lung cancer (NSCLC).

[0476] 9. Any of the preceding embodiments, wherein said patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than about 2 mg/L before first administration of said IL-1β binding antibody or functional fragment thereof.

[0477] 10. Any of the preceding embodiments, wherein said patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than 4 mg/L before first administration of said IL-1β binding antibody or functional fragment thereof.

[0478] 11. Any of the preceding embodiments, wherein said patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than 10 mg/L before first administration of said IL-1β binding antibody or functional fragment thereof.

[0479] 12. Any of the preceding embodiments, wherein the high sensitivity C-reactive protein (hsCRP) level of said patient has reduced to below about 3.5 mg/L assessed at least about 3 months after first administration of the IL-1β binding antibody or functional fragment thereof.

[0480] 13. Any of the preceding embodiments, wherein the high sensitivity C-reactive protein (hsCRP) level of said patient has reduced to below about 2.3 mg/L, preferably to below about 2 mg/L, preferably to below about 1.8 mg/L, assessed at least about 3 months after first administration of the IL-1β binding antibody or functional fragment thereof.

[0481] 14. Any of the preceding embodiments, wherein the high sensitivity C-reactive protein (hsCRP) level of said patient has reduced by at least 20% compared to baseline assessed at least about 3 months after first administration of the IL-1β binding antibody or functional fragment thereof.

[0482] 15. Any of the preceding embodiments, wherein the interleukin-6 (IL-6) level of said patient has reduced by at least 20% compared to baseline assessed at least about 3 months after first administration of the IL-1β binding antibody or functional fragment thereof.

[0483] 16. Any of the preceding embodiments, wherein said use comprises administering a dose of about 90 mg to about 450 mg of the IL-1β binding antibody or a functional fragment thereof per treatment.

[0484] 17. Any of the preceding embodiments, wherein said use comprises administering said IL-1β binding antibody or a functional fragment thereof every two, three or four weeks (monthly).

[0485] 18. Any of the preceding embodiments, the second administration of said IL-1β binding antibody or a functional fragment thereof is at most two weeks, preferably two weeks apart from the first administration.

[0486] 19. Any of the preceding embodiments, wherein said IL-1β binding antibody is canakinumab.

[0487] 20. Any of the preceding embodiments comprising administering about 200 mg to about 450 mg canakinumab per treatment to said patient.

[0488] 21. Any of the preceding embodiments comprising administering at least 150 mg canakinumab per treatment to said patient.

[0489] 22. The embodiments set forth in 19 or 21 comprising administering about 200 mg of canakinumab to said patient.

[0490] 23. The embodiments set forth in any one of 16-22, wherein canakinumab is administered every three weeks.

[0491] 24. The embodiments set forth in any one of 16-22, wherein canakinumab is administered every four weeks (monthly).

[0492] 25. The embodiments set forth in any one of 16-24, wherein canakinumab is administered subcutaneously.

[0493] 26. The embodiments set forth in any one of 16-25, wherein canakinumab is administered in a liquid form contained in a prefilled syringe or as a lyophilized form for reconstitution.

[0494] 27. Canakinumab for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis, preferably lung cancer, wherein said use comprises administering a dose of 200 mg of canakinumab subcutaneously every three week.

[0495] 28. The embodiments set forth in any one of 1-18, wherein said IL-1β binding antibody is gevokizumab (XOMA-052).

[0496] 29. The 28^{th} embodiment, wherein said use comprises administering 90 mg to 270 mg gevokizumab per treatment to said patient.

[0497] 30. The 28^{th} embodiment, comprising administering about 90 mg to about 120 mg of gevokizumab to said patient.

[0498] 31. The embodiments set forth in any one of 28-30, wherein gevokizumab is administered every three weeks.

[0499] 32. The embodiments set forth in any one of 28-30, wherein gevokizumab is administered every four weeks (monthly).

[0500] 33. The embodiments set forth in any one of 28-32, wherein gevokizumab is administered subcutaneously.

[0501] 34. The embodiments set forth in any one of 28-32, wherein gevokizumab is administered intravenously.

[0502] 35. Gevokizumab for use in a patient in need thereof in the treatment of a cancer having at least partial inflammatory basis, wherein said use comprises administering a dose of 120 mg of gevokizumab intravenously every four weeks (monthly).

[0503] 36. The embodiment set forth in 35, wherein said cancer having at least partial inflammatory basis is selected from the list consisting of lung cancer, especially NSCLC, colorectal cancer, melanoma, gastric cancer (including esophageal cancer), renal cell carcinoma (RCC), breast cancer, hepatocellular carcinoma (HCC), prostate cancer, bladder cancer, AML, multiple myeloma and pancreatic cancer.

[0504] 37. Any of the previous embodiments, wherein said IL-1β binding antibody or a functional fragment thereof is administered in combination with one or more chemotherapeutic agent; wherein preferably said IL-1β binding antibody or a functional fragment thereof is canakinumab or gevokizumab.

[0505] 38. The embodiment set forth in 37, wherein said one or more chemotherapeutic agent is the standard of care agent for said cancer.

[0506] 39. The embodiments set forth in 37 or 38, wherein said one or more chemotherapeutic agent is the standard of care agent for lung cancer, especially for NSCLC.

[0507] 40. The embodiments set forth in any one of 37 to 39, wherein said one or more chemotherapeutic agent is a platinum based chemotherapy or a platinum-based doublet chemotherapy (PT-DC).

[0508] 41. The embodiments set forth in any one of 37 to 40, wherein said one or more chemotherapeutic agent is a tyrosine kinase inhibitor.

[0509] 42. The embodiments set forth in any one of 37 to 41, wherein said one or more chemotherapeutic agent is a checkpoint inhibitor.

[0510] 43. The embodiments set forth in any one of 37 to 42, wherein said one or more chemotherapeutic agent is a PD-1 or PD-L1 inhibitor preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and spartalizumab (PDR-001).

[0511] 44. Any of the previous embodiments, wherein said IL-1β binding antibody or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of cancer having

at least a partial inflammatory basis in a subject after said cancer has been surgically removed.

[0512] 45. The embodiment set forth in 44, wherein said cancer with partial inflammatory basis is lung cancer.

[0513] 46. Any of the preceding embodiments, wherein said IL-1β binding antibody or a functional fragment thereof is used, alone or preferably in combination, as the first line treatment of lung cancer, especially NSCLC.

[0514] 47. Any of the preceding embodiments, wherein said IL-1β binding antibody or a functional fragment thereof is used, alone or preferrably in combination, as the second or third line treatment of lung cancer, especially NSCLC.

[0515] 48. The embodiments set forth in any one of 37 to 47, wherein said IL-1β binding antibody or a functional fragment thereof is canakinumab, wherein said patient is a smoker.

[0516] 49. An IL-1β binding antibody or a functional fragment thereof for use in the prevention of lung cancer in a patient, wherein said patient has a high sensitive C-reactive protein (hsCRP) level of equal or greater than 2 mg/L.

[0517] 50. The embodiment set forth in 49, wherein said hsCRP level is equal to or greater than 4 mg/L.

[0518] 51. The embodiments set forth in any one of 49-50, wherein said IL-1β binding antibody or a functional fragment thereof is canakinumab or a functional fragment thereof or gevokizumab or a functional fragment thereof

[0519] 52. Any of the preceding embodiments, wherein gevokizumab or a functional fragment thereof is administered in combination with one or more chemotherapeutic agent.

[0520] 53. The embodiment set forth in 52, wherein said one or more chemotherapeutic agent is the standard of care agent for colorectal cancer (CRC).

[0521] 54. The embodiments set forth in 52 or 53, wherein said one or more chemotherapeutic agent is a general cytotoxic agent, wherein preferably said general cytotoxic agent is selected from the list consisting of FOLFOX, FOLFIRI, capecitabine, 5-fluorouracil, irinotecan and oxaliplatin.

[0522] 55. The embodiments set forth in 52 or 53, wherein said one or more chemotherapeutic agent is a VEGF inhibitor, wherein preferably said VEGF inhibitor is selected from the list consisting of bevacizumab, ramucirumab and ziv-aflibercept.

[0523] 56. The embodiments set forth in any one of 52 to 55, wherein gevokizumab or a functional fragment thereof is administered in combination with FOLFIRI plus bevacizumab or FOLFOX plus bevacizumab.

[0524] 57. The embodiments set forth in any one of 52 to 56, wherein said one or more chemotherapeutic agent is a checkpoint inhibitor.

[0525] 58. The embodiments set forth in any one of 52 to 57, wherein said one or more chemotherapeutic agent is a PD-1 or PD-L1 inhibitor preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and spartalizumab (PDR-001).

[0526] 59. The embodiments set forth in any one of 52 to 58, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of colorectal cancer in a patient after said cancer has been surgically removed.

[0527] 60. The embodiments set forth in any one of 52 to 59, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, as the first line treatment of colorectal cancer.

[0528] 61. The embodiments set forth in any one of 52 to 59, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, as the second or third line treatment of colorectal cancer.

[0529] 62. The embodiment set forth in 52, wherein said one or more chemotherapeutic agent is the standard of care agent for renal cell carcinoma (RCC).

[0530] 63. The embodiments set forth in 52 or 62, wherein said one or more chemotherapeutic agent is a CTLA-4 checkpoint inhibitor, wherein preferably said CTLA-4 checkpoint inhibitor is ipilimumab.

[0531] 64. The embodiments set forth in any one of 52 and 62-63, wherein said one or more chemotherapeutic agent is everolimus.

[0532] 65. The embodiments set forth in any one of 52 and 62-64, wherein said one or more chemotherapeutic agent is a checkpoint inhibitor.

[0533] 66. The embodiments set forth in any one of 52 and 62-65, wherein said one or more chemotherapeutic agent is a PD-1 or PD-L1 inhibitor preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab and spartalizumab (PDR-001).

[0534] 67. The embodiments set forth in any one of 52 and 62-66, wherein said checkpoint inhibitor is nivolumab.

[0535] 68. The embodiments set forth in any one of 52 and 62-67, wherein said one or more chemotherapeutic agent are nivolumab plus ipilimumab.

[0536] 69. The embodiments set forth in any one of 52 and 62-68, wherein said one or more chemotherapeutic agent is cabozantinib.

[0537] 70. The embodiments set forth in any one of 52 and 62-69, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of renal cell carcinoma (RCC) in a patient after said cancer has been surgically removed.

[0538] 71. The embodiments set forth in any one of 52 and 62-70, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in first line treatment of renal cell carcinoma (RCC).

[0539] 72. The embodiments set forth in any one of 52 and 62-70, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in second or third line of renal cell carcinoma (RCC).

[0540] 73. The embodiment set forth in 52, wherein said one or more chemotherapeutic agent is the standard of care agent for gastric cancer (including esophageal cancer).

[0541] 74. The embodiments set forth in any one of 52 and 73, wherein said one or more chemotherapeutic agent is a mitotic inhibitor, preferably taxane, wherein preferably said taxane is selected from paclitaxel and docetaxel.

[0542] 75. The embodiments set forth in any one of 52 and 73-74, wherein said one or more chemotherapeutic agent wherein said one or more chemotherapeutic agent are paclitaxel and ramucirumab.

[0543] 76. The embodiments set forth in any one of 52 and 73-75, wherein said one or more chemotherapeutic agent is a checkpoint inhibitor.

[0544] 77. The embodiments set forth in any one of 52 and 73-76, wherein said one or more chemotherapeutic agent is a PD-1 or PD-L inhibitor preferably selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and spartalizumab (PDR-001).

[0545] 78. The embodiments set forth in 76 or 77, wherein said checkpoint inhibitor is nivolumab.

[0546] 79. The embodiments set forth in any one of 52 and 73-78, wherein said one or more chemotherapeutic agent are nivolumab and ipilimumab.

[0547] 80. The embodiments set forth in any one of 52 and 73-79, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, in the prevention of recurrence or relapse of in a patient after said gastric cancer (including esophageal cancer) has been surgically removed.

[0548] 81. The embodiments set forth in any one of 52 and 73-80, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, as the first line treatment of gastric cancer (including esophageal cancer).

[0549] 82. The embodiments set forth in any one of 52 and 73-81, wherein gevokizumab or a functional fragment thereof is used, alone or preferably in combination, as the second or third line treatment of gastric cancer (including esophageal cancer).

REFERENCES

[0550] 1. Coussens L M, Werb Z. Inflammation and cancer. Nature 2002; 420:860-7.

[0551] 2. Apte R N, Dotan S, Elkabets M, White M R, Reich E, Carmi Y, Song X, Dvozkin T, Krelin Y, Voronov E. The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. Cancer Metastasis Rev 2006; 25:387-408.

[0552] 3. Porta C, Larghi P, Rimoldi M, Totaro M G, Allavena P, Mantovani A, Sica A. Cellular and molecular pathways linking inflammation and cancer. Immunobiology 2009; 214:761-77.

[0553] 4. Balkwill F R, Mantovani A. Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 2012; 22:33-40.

[0554] 5. O'Callaghan D S, O'Donnell D, O'Connell F, O'Byrne K J. The role of inflammation in the pathogenesis of non-small cell lung cancer. J Thorac Oncol 2010; 5:2024-36.

[0555] 6. Lee J M, Yanagawa J, Peebles K A, Sharma S, Mao J T, Dubinett S M. Inflammation in lung carcinogenesis: new targets for lung cancer chemoprevention and treatment. Crit Rev Oncol Hematol 2008; 66:208-17.

[0556] 7. Dostert C, Petrilli V, Van Bruggen R, Steele C, Mossman B T, Tschopp J. Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica. Science 2008; 320:674-7.

[0557] 8. Gasse P, Mary C, Guenon I, Noulin N, Charron S, Schnyder-Candrian S, Schnyder B, Akira S, Quesniaux V F, Lagente V, Ryffel B, Couillin I. IL-1R1/MyD88 signaling and the inflammasome are essential in pulmonary inflammation and fibrosis in mice. J Clin Invest 2007; 117:3786-99.

[0558] 9. Voronov E, Shouval D S, Krelin Y, Cagnano E, Benharroch D, Iwakura Y, Dinarello C A, Apte R N. IL-1 is required for tumor invasiveness and angiogenesis. Proc Natl Acad Sci USA 2003; 100:2645-50.

[0559] 10. Dinarello C A, Simon A, van der Meer J W. Treating inflammation by blocking interleukin-1 in a broad spectrum of diseases. Nat Rev Drug Discov 2012; 11:633-52.

[0560] 11. Dinarello C A. Why not treat human cancer with interleukin-1 blockade? Cancer Metastasis Rev 2010; 29:317-29.

[0561] 12. Apte R N, Voronov E. Is interleukin-1 a good or bad 'guy' in tumor immunobiology and immunotherapy? Immunol Rev 2008; 222:222-41.

[0562] 13. Lewis A M, Varghese S, Xu H, Alexander H R. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. J Transl Med 2006; 4:48.

[0563] 14. Ridker P M, Thuren T, Zalewski A, Libby P. Interleukin-10 inhibition and the prevention of recurrent cardiovascular events: rationale and design of the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS). Am Heart J 2011; 162:597-605.

[0564] 15. Ridker P M, Howard C P, Walter V, Everett B, Libby P, Hensen J, Thuren T. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation 2012; 126:2739-48.

[0565] 16. Siemes C, Visser L E, Coebergh J W, Splinter T A, Witteman J C, Uitterlinden A G, Hofman A, Pols H A, Stricker B H. C-reactive protein levels, variation in the C-reactive protein gene, and cancer risk: the Rotterdam Study. J Clin Oncol 2006; 24:5216-22.

[0566] 17. Allin K H, Bojesen S E, Nordestgaard B G. Baseline C-reactive protein is associated with incident cancer and survival in patients with cancer. J Clin Oncol 2009; 27:2217-24.

[0567] 18. Chaturvedi A K, Caporaso N E, Katki H A, Wong H L, Chatterjee N, Pine S R, Chanock S J, Goedert J J, Engels E A. C-reactive protein and risk of lung cancer. J Clin Oncol 2010; 28:2719-26.

[0568] 19. Ridker P M, Howard C P, Walter V, Everett B, Libby P, Hensen J, et al. Effects of interleukin-1β inhibition with canakinumab on hemoglobin A1c, lipids, C-reactive protein, interleukin-6, and fibrinogen: a phase IIb randomized, placebo-controlled trial. Circulation. 2012; 126:2739-48.

[0569] 20. Ridker et al, CANTOS CVD manuscript

[0570] 21. Carmi Y, Rinott G, Dotan S, Elkabets M, Rider P, Voronov E, Apte R N. Microenvironmental-derived IL-1 and IL-17 interact in the control of lung metastasis. J Immunol 2011; 186:3462-3471.

[0571] 22. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357:539-45.

[0572] 23. Cuzick J, Otto F, Baron J A, Brown P H, Burn J, Greenwald P, Jankowski J, La Vecchia C, Meyskens F, Senn H J, Thun M. Aspirin and non-steroidal anti-inflammatory drugs for cancer prevention: an international consensus statement. Lancet Oncol 2009; 10:501-7.

[0573] 24. Rothwell P M, Fowkes F G, Belch J F, Ogawa H, Warlow C P, Meade T W. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. Lancet 2011; 377:31-41.

[0574] 25. Lust J A, Lacy M Q, Zeldenrust S R, Dispenzieri A, Gertz M A, Witzig T E, Kumar S, Hayman S R, Russell S J, Buadi F K, Geyer S M, Campbell M E, Kyle R A, Rajkumar S V, Greipp P R, Kline M P, Xiong Y, Moon-Tasson L L, Donovan K A. Induction of a chronic disease state in patients with smoldering or indolent multiple myeloma by targeting interleukin 1{β}-induced interleukin 6 production and the myeloma proliferative component. Mayo Clin Proc 2009; 84:114-22.

[0575] 26. Hong D S, Hui D, Bruera E, Janku F, Naing A, Falchook G S, Piha-Paul S, Wheler J J, Fu S, Tsimberidou A M, Stecher M, Mohanty P, Simard J, Kurzrock R. MABp1, a first-in-class true human antibody targeting interleukin-1alpha in refractory cancers: an open-label, phase 1 dose-escalation and expansion study. Lancet Oncol 2014; 15:656-66.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 1010

<210> SEQ ID NO 1

<400> SEQUENCE: 1

000

<210> SEQ ID NO 2

<400> SEQUENCE: 2

000

<210> SEQ ID NO 3

<400> SEQUENCE: 3

000

<210> SEQ ID NO 4

<400> SEQUENCE: 4

000

<210> SEQ ID NO 5

<400> SEQUENCE: 5

000

<210> SEQ ID NO 6

<400> SEQUENCE: 6

000

<210> SEQ ID NO 7

<400> SEQUENCE: 7

000

<210> SEQ ID NO 8

<400> SEQUENCE: 8

000

<210> SEQ ID NO 9

<400> SEQUENCE: 9

-continued

000

<210> SEQ ID NO 10

<400> SEQUENCE: 10

000

<210> SEQ ID NO 11

<400> SEQUENCE: 11

000

<210> SEQ ID NO 12

<400> SEQUENCE: 12

000

<210> SEQ ID NO 13

<400> SEQUENCE: 13

000

<210> SEQ ID NO 14

<400> SEQUENCE: 14

000

<210> SEQ ID NO 15

<400> SEQUENCE: 15

000

<210> SEQ ID NO 16

<400> SEQUENCE: 16

000

<210> SEQ ID NO 17

<400> SEQUENCE: 17

000

<210> SEQ ID NO 18

<400> SEQUENCE: 18

000

<210> SEQ ID NO 19

<400> SEQUENCE: 19

000

<210> SEQ ID NO 20

-continued

<400> SEQUENCE: 20

000

<210> SEQ ID NO 21

<400> SEQUENCE: 21

000

<210> SEQ ID NO 22

<400> SEQUENCE: 22

000

<210> SEQ ID NO 23

<400> SEQUENCE: 23

000

<210> SEQ ID NO 24

<400> SEQUENCE: 24

000

<210> SEQ ID NO 25

<400> SEQUENCE: 25

000

<210> SEQ ID NO 26

<400> SEQUENCE: 26

000

<210> SEQ ID NO 27

<400> SEQUENCE: 27

000

<210> SEQ ID NO 28

<400> SEQUENCE: 28

000

<210> SEQ ID NO 29

<400> SEQUENCE: 29

000

<210> SEQ ID NO 30

<400> SEQUENCE: 30

000

<210> SEQ ID NO 31

-continued

<400> SEQUENCE: 31

000

<210> SEQ ID NO 32

<400> SEQUENCE: 32

000

<210> SEQ ID NO 33

<400> SEQUENCE: 33

000

<210> SEQ ID NO 34

<400> SEQUENCE: 34

000

<210> SEQ ID NO 35

<400> SEQUENCE: 35

000

<210> SEQ ID NO 36

<400> SEQUENCE: 36

000

<210> SEQ ID NO 37

<400> SEQUENCE: 37

000

<210> SEQ ID NO 38

<400> SEQUENCE: 38

000

<210> SEQ ID NO 39

<400> SEQUENCE: 39

000

<210> SEQ ID NO 40

<400> SEQUENCE: 40

000

<210> SEQ ID NO 41

<400> SEQUENCE: 41

000

-continued

<210> SEQ ID NO 42

<400> SEQUENCE: 42

000

<210> SEQ ID NO 43

<400> SEQUENCE: 43

000

<210> SEQ ID NO 44

<400> SEQUENCE: 44

000

<210> SEQ ID NO 45

<400> SEQUENCE: 45

000

<210> SEQ ID NO 46

<400> SEQUENCE: 46

000

<210> SEQ ID NO 47

<400> SEQUENCE: 47

000

<210> SEQ ID NO 48

<400> SEQUENCE: 48

000

<210> SEQ ID NO 49

<400> SEQUENCE: 49

000

<210> SEQ ID NO 50

<400> SEQUENCE: 50

000

<210> SEQ ID NO 51

<400> SEQUENCE: 51

000

<210> SEQ ID NO 52

<400> SEQUENCE: 52

000

-continued

<210> SEQ ID NO 53

<400> SEQUENCE: 53

000

<210> SEQ ID NO 54

<400> SEQUENCE: 54

000

<210> SEQ ID NO 55

<400> SEQUENCE: 55

000

<210> SEQ ID NO 56

<400> SEQUENCE: 56

000

<210> SEQ ID NO 57

<400> SEQUENCE: 57

000

<210> SEQ ID NO 58

<400> SEQUENCE: 58

000

<210> SEQ ID NO 59

<400> SEQUENCE: 59

000

<210> SEQ ID NO 60

<400> SEQUENCE: 60

000

<210> SEQ ID NO 61

<400> SEQUENCE: 61

000

<210> SEQ ID NO 62

<400> SEQUENCE: 62

000

<210> SEQ ID NO 63

<400> SEQUENCE: 63

000

-continued

<210> SEQ ID NO 64

<400> SEQUENCE: 64

000

<210> SEQ ID NO 65

<400> SEQUENCE: 65

000

<210> SEQ ID NO 66

<400> SEQUENCE: 66

000

<210> SEQ ID NO 67

<400> SEQUENCE: 67

000

<210> SEQ ID NO 68

<400> SEQUENCE: 68

000

<210> SEQ ID NO 69

<400> SEQUENCE: 69

000

<210> SEQ ID NO 70

<400> SEQUENCE: 70

000

<210> SEQ ID NO 71

<400> SEQUENCE: 71

000

<210> SEQ ID NO 72

<400> SEQUENCE: 72

000

<210> SEQ ID NO 73

<400> SEQUENCE: 73

000

<210> SEQ ID NO 74

<400> SEQUENCE: 74

-continued

000

<210> SEQ ID NO 75

<400> SEQUENCE: 75

000

<210> SEQ ID NO 76

<400> SEQUENCE: 76

000

<210> SEQ ID NO 77

<400> SEQUENCE: 77

000

<210> SEQ ID NO 78

<400> SEQUENCE: 78

000

<210> SEQ ID NO 79

<400> SEQUENCE: 79

000

<210> SEQ ID NO 80

<400> SEQUENCE: 80

000

<210> SEQ ID NO 81

<400> SEQUENCE: 81

000

<210> SEQ ID NO 82

<400> SEQUENCE: 82

000

<210> SEQ ID NO 83

<400> SEQUENCE: 83

000

<210> SEQ ID NO 84

<400> SEQUENCE: 84

000

<210> SEQ ID NO 85

<400> SEQUENCE: 85

-continued

000

<210> SEQ ID NO 86

<400> SEQUENCE: 86

000

<210> SEQ ID NO 87

<400> SEQUENCE: 87

000

<210> SEQ ID NO 88

<400> SEQUENCE: 88

000

<210> SEQ ID NO 89

<400> SEQUENCE: 89

000

<210> SEQ ID NO 90

<400> SEQUENCE: 90

000

<210> SEQ ID NO 91

<400> SEQUENCE: 91

000

<210> SEQ ID NO 92

<400> SEQUENCE: 92

000

<210> SEQ ID NO 93

<400> SEQUENCE: 93

000

<210> SEQ ID NO 94

<400> SEQUENCE: 94

000

<210> SEQ ID NO 95

<400> SEQUENCE: 95

000

<210> SEQ ID NO 96

-continued

<400> SEQUENCE: 96

000

<210> SEQ ID NO 97

<400> SEQUENCE: 97

000

<210> SEQ ID NO 98

<400> SEQUENCE: 98

000

<210> SEQ ID NO 99

<400> SEQUENCE: 99

000

<210> SEQ ID NO 100

<400> SEQUENCE: 100

000

<210> SEQ ID NO 101

<400> SEQUENCE: 101

000

<210> SEQ ID NO 102

<400> SEQUENCE: 102

000

<210> SEQ ID NO 103

<400> SEQUENCE: 103

000

<210> SEQ ID NO 104

<400> SEQUENCE: 104

000

<210> SEQ ID NO 105

<400> SEQUENCE: 105

000

<210> SEQ ID NO 106

<400> SEQUENCE: 106

000

<210> SEQ ID NO 107

-continued

<400> SEQUENCE: 107

000

<210> SEQ ID NO 108

<400> SEQUENCE: 108

000

<210> SEQ ID NO 109

<400> SEQUENCE: 109

000

<210> SEQ ID NO 110

<400> SEQUENCE: 110

000

<210> SEQ ID NO 111

<400> SEQUENCE: 111

000

<210> SEQ ID NO 112

<400> SEQUENCE: 112

000

<210> SEQ ID NO 113

<400> SEQUENCE: 113

000

<210> SEQ ID NO 114

<400> SEQUENCE: 114

000

<210> SEQ ID NO 115

<400> SEQUENCE: 115

000

<210> SEQ ID NO 116

<400> SEQUENCE: 116

000

<210> SEQ ID NO 117

<400> SEQUENCE: 117

000

-continued

<210> SEQ ID NO 118

<400> SEQUENCE: 118

000

<210> SEQ ID NO 119

<400> SEQUENCE: 119

000

<210> SEQ ID NO 120

<400> SEQUENCE: 120

000

<210> SEQ ID NO 121

<400> SEQUENCE: 121

000

<210> SEQ ID NO 122

<400> SEQUENCE: 122

000

<210> SEQ ID NO 123

<400> SEQUENCE: 123

000

<210> SEQ ID NO 124

<400> SEQUENCE: 124

000

<210> SEQ ID NO 125

<400> SEQUENCE: 125

000

<210> SEQ ID NO 126

<400> SEQUENCE: 126

000

<210> SEQ ID NO 127

<400> SEQUENCE: 127

000

<210> SEQ ID NO 128

<400> SEQUENCE: 128

000

-continued

<210> SEQ ID NO 129

<400> SEQUENCE: 129

000

<210> SEQ ID NO 130

<400> SEQUENCE: 130

000

<210> SEQ ID NO 131

<400> SEQUENCE: 131

000

<210> SEQ ID NO 132

<400> SEQUENCE: 132

000

<210> SEQ ID NO 133

<400> SEQUENCE: 133

000

<210> SEQ ID NO 134

<400> SEQUENCE: 134

000

<210> SEQ ID NO 135

<400> SEQUENCE: 135

000

<210> SEQ ID NO 136

<400> SEQUENCE: 136

000

<210> SEQ ID NO 137

<400> SEQUENCE: 137

000

<210> SEQ ID NO 138

<400> SEQUENCE: 138

000

<210> SEQ ID NO 139

<400> SEQUENCE: 139

000

-continued

<210> SEQ ID NO 140

<400> SEQUENCE: 140

000

<210> SEQ ID NO 141

<400> SEQUENCE: 141

000

<210> SEQ ID NO 142

<400> SEQUENCE: 142

000

<210> SEQ ID NO 143

<400> SEQUENCE: 143

000

<210> SEQ ID NO 144

<400> SEQUENCE: 144

000

<210> SEQ ID NO 145

<400> SEQUENCE: 145

000

<210> SEQ ID NO 146

<400> SEQUENCE: 146

000

<210> SEQ ID NO 147

<400> SEQUENCE: 147

000

<210> SEQ ID NO 148

<400> SEQUENCE: 148

000

<210> SEQ ID NO 149

<400> SEQUENCE: 149

000

<210> SEQ ID NO 150

<400> SEQUENCE: 150

-continued

000

<210> SEQ ID NO 151

<400> SEQUENCE: 151

000

<210> SEQ ID NO 152

<400> SEQUENCE: 152

000

<210> SEQ ID NO 153

<400> SEQUENCE: 153

000

<210> SEQ ID NO 154

<400> SEQUENCE: 154

000

<210> SEQ ID NO 155

<400> SEQUENCE: 155

000

<210> SEQ ID NO 156

<400> SEQUENCE: 156

000

<210> SEQ ID NO 157

<400> SEQUENCE: 157

000

<210> SEQ ID NO 158

<400> SEQUENCE: 158

000

<210> SEQ ID NO 159

<400> SEQUENCE: 159

000

<210> SEQ ID NO 160

<400> SEQUENCE: 160

000

<210> SEQ ID NO 161

<400> SEQUENCE: 161

-continued

000

<210> SEQ ID NO 162

<400> SEQUENCE: 162

000

<210> SEQ ID NO 163

<400> SEQUENCE: 163

000

<210> SEQ ID NO 164

<400> SEQUENCE: 164

000

<210> SEQ ID NO 165

<400> SEQUENCE: 165

000

<210> SEQ ID NO 166

<400> SEQUENCE: 166

000

<210> SEQ ID NO 167

<400> SEQUENCE: 167

000

<210> SEQ ID NO 168

<400> SEQUENCE: 168

000

<210> SEQ ID NO 169

<400> SEQUENCE: 169

000

<210> SEQ ID NO 170

<400> SEQUENCE: 170

000

<210> SEQ ID NO 171

<400> SEQUENCE: 171

000

<210> SEQ ID NO 172

-continued

<400> SEQUENCE: 172

000

<210> SEQ ID NO 173

<400> SEQUENCE: 173

000

<210> SEQ ID NO 174

<400> SEQUENCE: 174

000

<210> SEQ ID NO 175

<400> SEQUENCE: 175

000

<210> SEQ ID NO 176

<400> SEQUENCE: 176

000

<210> SEQ ID NO 177

<400> SEQUENCE: 177

000

<210> SEQ ID NO 178

<400> SEQUENCE: 178

000

<210> SEQ ID NO 179

<400> SEQUENCE: 179

000

<210> SEQ ID NO 180

<400> SEQUENCE: 180

000

<210> SEQ ID NO 181

<400> SEQUENCE: 181

000

<210> SEQ ID NO 182

<400> SEQUENCE: 182

000

<210> SEQ ID NO 183

-continued

<400> SEQUENCE: 183

000

<210> SEQ ID NO 184

<400> SEQUENCE: 184

000

<210> SEQ ID NO 185

<400> SEQUENCE: 185

000

<210> SEQ ID NO 186

<400> SEQUENCE: 186

000

<210> SEQ ID NO 187

<400> SEQUENCE: 187

000

<210> SEQ ID NO 188

<400> SEQUENCE: 188

000

<210> SEQ ID NO 189

<400> SEQUENCE: 189

000

<210> SEQ ID NO 190

<400> SEQUENCE: 190

000

<210> SEQ ID NO 191

<400> SEQUENCE: 191

000

<210> SEQ ID NO 192

<400> SEQUENCE: 192

000

<210> SEQ ID NO 193

<400> SEQUENCE: 193

000

-continued

<210> SEQ ID NO 194

<400> SEQUENCE: 194

000

<210> SEQ ID NO 195

<400> SEQUENCE: 195

000

<210> SEQ ID NO 196

<400> SEQUENCE: 196

000

<210> SEQ ID NO 197

<400> SEQUENCE: 197

000

<210> SEQ ID NO 198

<400> SEQUENCE: 198

000

<210> SEQ ID NO 199

<400> SEQUENCE: 199

000

<210> SEQ ID NO 200

<400> SEQUENCE: 200

000

<210> SEQ ID NO 201

<400> SEQUENCE: 201

000

<210> SEQ ID NO 202

<400> SEQUENCE: 202

000

<210> SEQ ID NO 203

<400> SEQUENCE: 203

000

<210> SEQ ID NO 204

<400> SEQUENCE: 204

000

-continued

<210> SEQ ID NO 205

<400> SEQUENCE: 205

000

<210> SEQ ID NO 206

<400> SEQUENCE: 206

000

<210> SEQ ID NO 207

<400> SEQUENCE: 207

000

<210> SEQ ID NO 208

<400> SEQUENCE: 208

000

<210> SEQ ID NO 209

<400> SEQUENCE: 209

000

<210> SEQ ID NO 210

<400> SEQUENCE: 210

000

<210> SEQ ID NO 211

<400> SEQUENCE: 211

000

<210> SEQ ID NO 212

<400> SEQUENCE: 212

000

<210> SEQ ID NO 213

<400> SEQUENCE: 213

000

<210> SEQ ID NO 214

<400> SEQUENCE: 214

000

<210> SEQ ID NO 215

<400> SEQUENCE: 215

000

-continued

<210> SEQ ID NO 216

<400> SEQUENCE: 216

000

<210> SEQ ID NO 217

<400> SEQUENCE: 217

000

<210> SEQ ID NO 218

<400> SEQUENCE: 218

000

<210> SEQ ID NO 219

<400> SEQUENCE: 219

000

<210> SEQ ID NO 220

<400> SEQUENCE: 220

000

<210> SEQ ID NO 221

<400> SEQUENCE: 221

000

<210> SEQ ID NO 222

<400> SEQUENCE: 222

000

<210> SEQ ID NO 223

<400> SEQUENCE: 223

000

<210> SEQ ID NO 224

<400> SEQUENCE: 224

000

<210> SEQ ID NO 225

<400> SEQUENCE: 225

000

<210> SEQ ID NO 226

<400> SEQUENCE: 226

-continued

000

<210> SEQ ID NO 227

<400> SEQUENCE: 227

000

<210> SEQ ID NO 228

<400> SEQUENCE: 228

000

<210> SEQ ID NO 229

<400> SEQUENCE: 229

000

<210> SEQ ID NO 230

<400> SEQUENCE: 230

000

<210> SEQ ID NO 231

<400> SEQUENCE: 231

000

<210> SEQ ID NO 232

<400> SEQUENCE: 232

000

<210> SEQ ID NO 233

<400> SEQUENCE: 233

000

<210> SEQ ID NO 234

<400> SEQUENCE: 234

000

<210> SEQ ID NO 235

<400> SEQUENCE: 235

000

<210> SEQ ID NO 236

<400> SEQUENCE: 236

000

<210> SEQ ID NO 237

<400> SEQUENCE: 237

-continued

000

<210> SEQ ID NO 238

<400> SEQUENCE: 238

000

<210> SEQ ID NO 239

<400> SEQUENCE: 239

000

<210> SEQ ID NO 240

<400> SEQUENCE: 240

000

<210> SEQ ID NO 241

<400> SEQUENCE: 241

000

<210> SEQ ID NO 242

<400> SEQUENCE: 242

000

<210> SEQ ID NO 243

<400> SEQUENCE: 243

000

<210> SEQ ID NO 244

<400> SEQUENCE: 244

000

<210> SEQ ID NO 245

<400> SEQUENCE: 245

000

<210> SEQ ID NO 246

<400> SEQUENCE: 246

000

<210> SEQ ID NO 247

<400> SEQUENCE: 247

000

<210> SEQ ID NO 248

-continued

<400> SEQUENCE: 248

000

<210> SEQ ID NO 249

<400> SEQUENCE: 249

000

<210> SEQ ID NO 250

<400> SEQUENCE: 250

000

<210> SEQ ID NO 251

<400> SEQUENCE: 251

000

<210> SEQ ID NO 252

<400> SEQUENCE: 252

000

<210> SEQ ID NO 253

<400> SEQUENCE: 253

000

<210> SEQ ID NO 254

<400> SEQUENCE: 254

000

<210> SEQ ID NO 255

<400> SEQUENCE: 255

000

<210> SEQ ID NO 256

<400> SEQUENCE: 256

000

<210> SEQ ID NO 257

<400> SEQUENCE: 257

000

<210> SEQ ID NO 258

<400> SEQUENCE: 258

000

<210> SEQ ID NO 259

-continued

<400> SEQUENCE: 259

000

<210> SEQ ID NO 260

<400> SEQUENCE: 260

000

<210> SEQ ID NO 261

<400> SEQUENCE: 261

000

<210> SEQ ID NO 262

<400> SEQUENCE: 262

000

<210> SEQ ID NO 263

<400> SEQUENCE: 263

000

<210> SEQ ID NO 264

<400> SEQUENCE: 264

000

<210> SEQ ID NO 265

<400> SEQUENCE: 265

000

<210> SEQ ID NO 266

<400> SEQUENCE: 266

000

<210> SEQ ID NO 267

<400> SEQUENCE: 267

000

<210> SEQ ID NO 268

<400> SEQUENCE: 268

000

<210> SEQ ID NO 269

<400> SEQUENCE: 269

000

-continued

<210> SEQ ID NO 270

<400> SEQUENCE: 270

000

<210> SEQ ID NO 271

<400> SEQUENCE: 271

000

<210> SEQ ID NO 272

<400> SEQUENCE: 272

000

<210> SEQ ID NO 273

<400> SEQUENCE: 273

000

<210> SEQ ID NO 274

<400> SEQUENCE: 274

000

<210> SEQ ID NO 275

<400> SEQUENCE: 275

000

<210> SEQ ID NO 276

<400> SEQUENCE: 276

000

<210> SEQ ID NO 277

<400> SEQUENCE: 277

000

<210> SEQ ID NO 278

<400> SEQUENCE: 278

000

<210> SEQ ID NO 279

<400> SEQUENCE: 279

000

<210> SEQ ID NO 280

<400> SEQUENCE: 280

000

-continued

<210> SEQ ID NO 281

<400> SEQUENCE: 281

000

<210> SEQ ID NO 282

<400> SEQUENCE: 282

000

<210> SEQ ID NO 283

<400> SEQUENCE: 283

000

<210> SEQ ID NO 284

<400> SEQUENCE: 284

000

<210> SEQ ID NO 285

<400> SEQUENCE: 285

000

<210> SEQ ID NO 286

<400> SEQUENCE: 286

000

<210> SEQ ID NO 287

<400> SEQUENCE: 287

000

<210> SEQ ID NO 288

<400> SEQUENCE: 288

000

<210> SEQ ID NO 289

<400> SEQUENCE: 289

000

<210> SEQ ID NO 290

<400> SEQUENCE: 290

000

<210> SEQ ID NO 291

<400> SEQUENCE: 291

000

-continued

<210> SEQ ID NO 292

<400> SEQUENCE: 292

000

<210> SEQ ID NO 293

<400> SEQUENCE: 293

000

<210> SEQ ID NO 294

<400> SEQUENCE: 294

000

<210> SEQ ID NO 295

<400> SEQUENCE: 295

000

<210> SEQ ID NO 296

<400> SEQUENCE: 296

000

<210> SEQ ID NO 297

<400> SEQUENCE: 297

000

<210> SEQ ID NO 298

<400> SEQUENCE: 298

000

<210> SEQ ID NO 299

<400> SEQUENCE: 299

000

<210> SEQ ID NO 300

<400> SEQUENCE: 300

000

<210> SEQ ID NO 301

<400> SEQUENCE: 301

000

<210> SEQ ID NO 302

<400> SEQUENCE: 302

-continued

000

<210> SEQ ID NO 303

<400> SEQUENCE: 303

000

<210> SEQ ID NO 304

<400> SEQUENCE: 304

000

<210> SEQ ID NO 305

<400> SEQUENCE: 305

000

<210> SEQ ID NO 306

<400> SEQUENCE: 306

000

<210> SEQ ID NO 307

<400> SEQUENCE: 307

000

<210> SEQ ID NO 308

<400> SEQUENCE: 308

000

<210> SEQ ID NO 309

<400> SEQUENCE: 309

000

<210> SEQ ID NO 310

<400> SEQUENCE: 310

000

<210> SEQ ID NO 311

<400> SEQUENCE: 311

000

<210> SEQ ID NO 312

<400> SEQUENCE: 312

000

<210> SEQ ID NO 313

<400> SEQUENCE: 313

-continued

000

<210> SEQ ID NO 314

<400> SEQUENCE: 314

000

<210> SEQ ID NO 315

<400> SEQUENCE: 315

000

<210> SEQ ID NO 316

<400> SEQUENCE: 316

000

<210> SEQ ID NO 317

<400> SEQUENCE: 317

000

<210> SEQ ID NO 318

<400> SEQUENCE: 318

000

<210> SEQ ID NO 319

<400> SEQUENCE: 319

000

<210> SEQ ID NO 320

<400> SEQUENCE: 320

000

<210> SEQ ID NO 321

<400> SEQUENCE: 321

000

<210> SEQ ID NO 322

<400> SEQUENCE: 322

000

<210> SEQ ID NO 323

<400> SEQUENCE: 323

000

<210> SEQ ID NO 324

-continued

<400> SEQUENCE: 324

000

<210> SEQ ID NO 325

<400> SEQUENCE: 325

000

<210> SEQ ID NO 326

<400> SEQUENCE: 326

000

<210> SEQ ID NO 327

<400> SEQUENCE: 327

000

<210> SEQ ID NO 328

<400> SEQUENCE: 328

000

<210> SEQ ID NO 329

<400> SEQUENCE: 329

000

<210> SEQ ID NO 330

<400> SEQUENCE: 330

000

<210> SEQ ID NO 331

<400> SEQUENCE: 331

000

<210> SEQ ID NO 332

<400> SEQUENCE: 332

000

<210> SEQ ID NO 333

<400> SEQUENCE: 333

000

<210> SEQ ID NO 334

<400> SEQUENCE: 334

000

<210> SEQ ID NO 335

-continued

<400> SEQUENCE: 335

000

<210> SEQ ID NO 336

<400> SEQUENCE: 336

000

<210> SEQ ID NO 337

<400> SEQUENCE: 337

000

<210> SEQ ID NO 338

<400> SEQUENCE: 338

000

<210> SEQ ID NO 339

<400> SEQUENCE: 339

000

<210> SEQ ID NO 340

<400> SEQUENCE: 340

000

<210> SEQ ID NO 341

<400> SEQUENCE: 341

000

<210> SEQ ID NO 342

<400> SEQUENCE: 342

000

<210> SEQ ID NO 343

<400> SEQUENCE: 343

000

<210> SEQ ID NO 344

<400> SEQUENCE: 344

000

<210> SEQ ID NO 345

<400> SEQUENCE: 345

000

-continued

<210> SEQ ID NO 346

<400> SEQUENCE: 346

000

<210> SEQ ID NO 347

<400> SEQUENCE: 347

000

<210> SEQ ID NO 348

<400> SEQUENCE: 348

000

<210> SEQ ID NO 349

<400> SEQUENCE: 349

000

<210> SEQ ID NO 350

<400> SEQUENCE: 350

000

<210> SEQ ID NO 351

<400> SEQUENCE: 351

000

<210> SEQ ID NO 352

<400> SEQUENCE: 352

000

<210> SEQ ID NO 353

<400> SEQUENCE: 353

000

<210> SEQ ID NO 354

<400> SEQUENCE: 354

000

<210> SEQ ID NO 355

<400> SEQUENCE: 355

000

<210> SEQ ID NO 356

<400> SEQUENCE: 356

000

-continued

<210> SEQ ID NO 357

<400> SEQUENCE: 357

000

<210> SEQ ID NO 358

<400> SEQUENCE: 358

000

<210> SEQ ID NO 359

<400> SEQUENCE: 359

000

<210> SEQ ID NO 360

<400> SEQUENCE: 360

000

<210> SEQ ID NO 361

<400> SEQUENCE: 361

000

<210> SEQ ID NO 362

<400> SEQUENCE: 362

000

<210> SEQ ID NO 363

<400> SEQUENCE: 363

000

<210> SEQ ID NO 364

<400> SEQUENCE: 364

000

<210> SEQ ID NO 365

<400> SEQUENCE: 365

000

<210> SEQ ID NO 366

<400> SEQUENCE: 366

000

<210> SEQ ID NO 367

<400> SEQUENCE: 367

000

-continued

<210> SEQ ID NO 368

<400> SEQUENCE: 368

000

<210> SEQ ID NO 369

<400> SEQUENCE: 369

000

<210> SEQ ID NO 370

<400> SEQUENCE: 370

000

<210> SEQ ID NO 371

<400> SEQUENCE: 371

000

<210> SEQ ID NO 372

<400> SEQUENCE: 372

000

<210> SEQ ID NO 373

<400> SEQUENCE: 373

000

<210> SEQ ID NO 374

<400> SEQUENCE: 374

000

<210> SEQ ID NO 375

<400> SEQUENCE: 375

000

<210> SEQ ID NO 376

<400> SEQUENCE: 376

000

<210> SEQ ID NO 377

<400> SEQUENCE: 377

000

<210> SEQ ID NO 378

<400> SEQUENCE: 378

-continued

000

<210> SEQ ID NO 379

<400> SEQUENCE: 379

000

<210> SEQ ID NO 380

<400> SEQUENCE: 380

000

<210> SEQ ID NO 381

<400> SEQUENCE: 381

000

<210> SEQ ID NO 382

<400> SEQUENCE: 382

000

<210> SEQ ID NO 383

<400> SEQUENCE: 383

000

<210> SEQ ID NO 384

<400> SEQUENCE: 384

000

<210> SEQ ID NO 385

<400> SEQUENCE: 385

000

<210> SEQ ID NO 386

<400> SEQUENCE: 386

000

<210> SEQ ID NO 387

<400> SEQUENCE: 387

000

<210> SEQ ID NO 388

<400> SEQUENCE: 388

000

<210> SEQ ID NO 389

<400> SEQUENCE: 389

-continued

000

<210> SEQ ID NO 390

<400> SEQUENCE: 390

000

<210> SEQ ID NO 391

<400> SEQUENCE: 391

000

<210> SEQ ID NO 392

<400> SEQUENCE: 392

000

<210> SEQ ID NO 393

<400> SEQUENCE: 393

000

<210> SEQ ID NO 394

<400> SEQUENCE: 394

000

<210> SEQ ID NO 395

<400> SEQUENCE: 395

000

<210> SEQ ID NO 396

<400> SEQUENCE: 396

000

<210> SEQ ID NO 397

<400> SEQUENCE: 397

000

<210> SEQ ID NO 398

<400> SEQUENCE: 398

000

<210> SEQ ID NO 399

<400> SEQUENCE: 399

000

<210> SEQ ID NO 400

-continued

<400> SEQUENCE: 400

000

<210> SEQ ID NO 401

<400> SEQUENCE: 401

000

<210> SEQ ID NO 402

<400> SEQUENCE: 402

000

<210> SEQ ID NO 403

<400> SEQUENCE: 403

000

<210> SEQ ID NO 404

<400> SEQUENCE: 404

000

<210> SEQ ID NO 405

<400> SEQUENCE: 405

000

<210> SEQ ID NO 406

<400> SEQUENCE: 406

000

<210> SEQ ID NO 407

<400> SEQUENCE: 407

000

<210> SEQ ID NO 408

<400> SEQUENCE: 408

000

<210> SEQ ID NO 409

<400> SEQUENCE: 409

000

<210> SEQ ID NO 410

<400> SEQUENCE: 410

000

<210> SEQ ID NO 411

-continued

<400> SEQUENCE: 411

000

<210> SEQ ID NO 412

<400> SEQUENCE: 412

000

<210> SEQ ID NO 413

<400> SEQUENCE: 413

000

<210> SEQ ID NO 414

<400> SEQUENCE: 414

000

<210> SEQ ID NO 415

<400> SEQUENCE: 415

000

<210> SEQ ID NO 416

<400> SEQUENCE: 416

000

<210> SEQ ID NO 417

<400> SEQUENCE: 417

000

<210> SEQ ID NO 418

<400> SEQUENCE: 418

000

<210> SEQ ID NO 419

<400> SEQUENCE: 419

000

<210> SEQ ID NO 420

<400> SEQUENCE: 420

000

<210> SEQ ID NO 421

<400> SEQUENCE: 421

000

-continued

<210> SEQ ID NO 422

<400> SEQUENCE: 422

000

<210> SEQ ID NO 423

<400> SEQUENCE: 423

000

<210> SEQ ID NO 424

<400> SEQUENCE: 424

000

<210> SEQ ID NO 425

<400> SEQUENCE: 425

000

<210> SEQ ID NO 426

<400> SEQUENCE: 426

000

<210> SEQ ID NO 427

<400> SEQUENCE: 427

000

<210> SEQ ID NO 428

<400> SEQUENCE: 428

000

<210> SEQ ID NO 429

<400> SEQUENCE: 429

000

<210> SEQ ID NO 430

<400> SEQUENCE: 430

000

<210> SEQ ID NO 431

<400> SEQUENCE: 431

000

<210> SEQ ID NO 432

<400> SEQUENCE: 432

000

-continued

<210> SEQ ID NO 433

<400> SEQUENCE: 433

000

<210> SEQ ID NO 434

<400> SEQUENCE: 434

000

<210> SEQ ID NO 435

<400> SEQUENCE: 435

000

<210> SEQ ID NO 436

<400> SEQUENCE: 436

000

<210> SEQ ID NO 437

<400> SEQUENCE: 437

000

<210> SEQ ID NO 438

<400> SEQUENCE: 438

000

<210> SEQ ID NO 439

<400> SEQUENCE: 439

000

<210> SEQ ID NO 440

<400> SEQUENCE: 440

000

<210> SEQ ID NO 441

<400> SEQUENCE: 441

000

<210> SEQ ID NO 442

<400> SEQUENCE: 442

000

<210> SEQ ID NO 443

<400> SEQUENCE: 443

000

-continued

<210> SEQ ID NO 444

<400> SEQUENCE: 444

000

<210> SEQ ID NO 445

<400> SEQUENCE: 445

000

<210> SEQ ID NO 446

<400> SEQUENCE: 446

000

<210> SEQ ID NO 447

<400> SEQUENCE: 447

000

<210> SEQ ID NO 448

<400> SEQUENCE: 448

000

<210> SEQ ID NO 449

<400> SEQUENCE: 449

000

<210> SEQ ID NO 450

<400> SEQUENCE: 450

000

<210> SEQ ID NO 451

<400> SEQUENCE: 451

000

<210> SEQ ID NO 452

<400> SEQUENCE: 452

000

<210> SEQ ID NO 453

<400> SEQUENCE: 453

000

<210> SEQ ID NO 454

<400> SEQUENCE: 454

-continued

000

<210> SEQ ID NO 455

<400> SEQUENCE: 455

000

<210> SEQ ID NO 456

<400> SEQUENCE: 456

000

<210> SEQ ID NO 457

<400> SEQUENCE: 457

000

<210> SEQ ID NO 458

<400> SEQUENCE: 458

000

<210> SEQ ID NO 459

<400> SEQUENCE: 459

000

<210> SEQ ID NO 460

<400> SEQUENCE: 460

000

<210> SEQ ID NO 461

<400> SEQUENCE: 461

000

<210> SEQ ID NO 462

<400> SEQUENCE: 462

000

<210> SEQ ID NO 463

<400> SEQUENCE: 463

000

<210> SEQ ID NO 464

<400> SEQUENCE: 464

000

<210> SEQ ID NO 465

<400> SEQUENCE: 465

-continued

000

<210> SEQ ID NO 466

<400> SEQUENCE: 466

000

<210> SEQ ID NO 467

<400> SEQUENCE: 467

000

<210> SEQ ID NO 468

<400> SEQUENCE: 468

000

<210> SEQ ID NO 469

<400> SEQUENCE: 469

000

<210> SEQ ID NO 470

<400> SEQUENCE: 470

000

<210> SEQ ID NO 471

<400> SEQUENCE: 471

000

<210> SEQ ID NO 472

<400> SEQUENCE: 472

000

<210> SEQ ID NO 473

<400> SEQUENCE: 473

000

<210> SEQ ID NO 474

<400> SEQUENCE: 474

000

<210> SEQ ID NO 475

<400> SEQUENCE: 475

000

<210> SEQ ID NO 476

-continued

<400> SEQUENCE: 476

000

<210> SEQ ID NO 477

<400> SEQUENCE: 477

000

<210> SEQ ID NO 478

<400> SEQUENCE: 478

000

<210> SEQ ID NO 479

<400> SEQUENCE: 479

000

<210> SEQ ID NO 480

<400> SEQUENCE: 480

000

<210> SEQ ID NO 481

<400> SEQUENCE: 481

000

<210> SEQ ID NO 482

<400> SEQUENCE: 482

000

<210> SEQ ID NO 483

<400> SEQUENCE: 483

000

<210> SEQ ID NO 484

<400> SEQUENCE: 484

000

<210> SEQ ID NO 485

<400> SEQUENCE: 485

000

<210> SEQ ID NO 486

<400> SEQUENCE: 486

000

<210> SEQ ID NO 487

-continued

<400> SEQUENCE: 487

000

<210> SEQ ID NO 488

<400> SEQUENCE: 488

000

<210> SEQ ID NO 489

<400> SEQUENCE: 489

000

<210> SEQ ID NO 490

<400> SEQUENCE: 490

000

<210> SEQ ID NO 491

<400> SEQUENCE: 491

000

<210> SEQ ID NO 492

<400> SEQUENCE: 492

000

<210> SEQ ID NO 493

<400> SEQUENCE: 493

000

<210> SEQ ID NO 494

<400> SEQUENCE: 494

000

<210> SEQ ID NO 495

<400> SEQUENCE: 495

000

<210> SEQ ID NO 496

<400> SEQUENCE: 496

000

<210> SEQ ID NO 497

<400> SEQUENCE: 497

000

-continued

<210> SEQ ID NO 498

<400> SEQUENCE: 498

000

<210> SEQ ID NO 499

<400> SEQUENCE: 499

000

<210> SEQ ID NO 500

<400> SEQUENCE: 500

000

<210> SEQ ID NO 501

<400> SEQUENCE: 501

000

<210> SEQ ID NO 502

<400> SEQUENCE: 502

000

<210> SEQ ID NO 503

<400> SEQUENCE: 503

000

<210> SEQ ID NO 504

<400> SEQUENCE: 504

000

<210> SEQ ID NO 505

<400> SEQUENCE: 505

000

<210> SEQ ID NO 506
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 506

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Glu
1 5 10 15

Ser Leu Arg Ile Ser Cys Lys Gly Ser Gly Tyr Thr Phe Thr Thr Tyr
20 25 30

Trp Met His Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

-continued

```
Gly Asn Ile Tyr Pro Gly Thr Gly Gly Ser Asn Phe Asp Glu Lys Phe
    50                  55                  60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Trp Thr Thr Gly Thr Gly Ala Tyr Trp Gly Gln Gly Thr Thr
            100                 105                 110

Val Thr Val Ser Ser
        115
```

<210> SEQ ID NO 507

<400> SEQUENCE: 507

000

<210> SEQ ID NO 508

<400> SEQUENCE: 508

000

<210> SEQ ID NO 509

<400> SEQUENCE: 509

000

<210> SEQ ID NO 510

<400> SEQUENCE: 510

000

<210> SEQ ID NO 511

<400> SEQUENCE: 511

000

<210> SEQ ID NO 512

<400> SEQUENCE: 512

000

<210> SEQ ID NO 513

<400> SEQUENCE: 513

000

<210> SEQ ID NO 514

<400> SEQUENCE: 514

000

<210> SEQ ID NO 515

<400> SEQUENCE: 515

-continued

000

<210> SEQ ID NO 516
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 516

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys
35 40 45

Ala Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65 70 75 80

Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Asn
85 90 95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> SEQ ID NO 517

<400> SEQUENCE: 517

000

<210> SEQ ID NO 518

<400> SEQUENCE: 518

000

<210> SEQ ID NO 519

<400> SEQUENCE: 519

000

<210> SEQ ID NO 520
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 520

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ser Ser Gln Ser Leu Leu Asp Ser
20 25 30

-continued

```
Gly Asn Gln Lys Asn Phe Leu Thr Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ala Pro Arg Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
    50                  55                  60

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr
65                  70                  75                  80

Ile Ser Ser Leu Glu Ala Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Asn
                85                  90                  95

Asp Tyr Ser Tyr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
            100                 105                 110

Lys
```

<210> SEQ ID NO 521

<400> SEQUENCE: 521

000

<210> SEQ ID NO 522

<400> SEQUENCE: 522

000

<210> SEQ ID NO 523

<400> SEQUENCE: 523

000

<210> SEQ ID NO 524

<400> SEQUENCE: 524

000

<210> SEQ ID NO 525

<400> SEQUENCE: 525

000

<210> SEQ ID NO 526

<400> SEQUENCE: 526

000

<210> SEQ ID NO 527

<400> SEQUENCE: 527

000

<210> SEQ ID NO 528

<400> SEQUENCE: 528

000

<210> SEQ ID NO 529

-continued

<400> SEQUENCE: 529

000

<210> SEQ ID NO 530

<400> SEQUENCE: 530

000

<210> SEQ ID NO 531

<400> SEQUENCE: 531

000

<210> SEQ ID NO 532

<400> SEQUENCE: 532

000

<210> SEQ ID NO 533

<400> SEQUENCE: 533

000

<210> SEQ ID NO 534

<400> SEQUENCE: 534

000

<210> SEQ ID NO 535

<400> SEQUENCE: 535

000

<210> SEQ ID NO 536

<400> SEQUENCE: 536

000

<210> SEQ ID NO 537

<400> SEQUENCE: 537

000

<210> SEQ ID NO 538

<400> SEQUENCE: 538

000

<210> SEQ ID NO 539

<400> SEQUENCE: 539

000

<210> SEQ ID NO 540

-continued

<400> SEQUENCE: 540

000

<210> SEQ ID NO 541

<400> SEQUENCE: 541

000

<210> SEQ ID NO 542

<400> SEQUENCE: 542

000

<210> SEQ ID NO 543

<400> SEQUENCE: 543

000

<210> SEQ ID NO 544

<400> SEQUENCE: 544

000

<210> SEQ ID NO 545

<400> SEQUENCE: 545

000

<210> SEQ ID NO 546

<400> SEQUENCE: 546

000

<210> SEQ ID NO 547

<400> SEQUENCE: 547

000

<210> SEQ ID NO 548

<400> SEQUENCE: 548

000

<210> SEQ ID NO 549

<400> SEQUENCE: 549

000

<210> SEQ ID NO 550

<400> SEQUENCE: 550

000

-continued

<210> SEQ ID NO 551

<400> SEQUENCE: 551

000

<210> SEQ ID NO 552

<400> SEQUENCE: 552

000

<210> SEQ ID NO 553

<400> SEQUENCE: 553

000

<210> SEQ ID NO 554

<400> SEQUENCE: 554

000

<210> SEQ ID NO 555

<400> SEQUENCE: 555

000

<210> SEQ ID NO 556

<400> SEQUENCE: 556

000

<210> SEQ ID NO 557

<400> SEQUENCE: 557

000

<210> SEQ ID NO 558

<400> SEQUENCE: 558

000

<210> SEQ ID NO 559

<400> SEQUENCE: 559

000

<210> SEQ ID NO 560

<400> SEQUENCE: 560

000

<210> SEQ ID NO 561

<400> SEQUENCE: 561

000

-continued

<210> SEQ ID NO 562

<400> SEQUENCE: 562

000

<210> SEQ ID NO 563

<400> SEQUENCE: 563

000

<210> SEQ ID NO 564

<400> SEQUENCE: 564

000

<210> SEQ ID NO 565

<400> SEQUENCE: 565

000

<210> SEQ ID NO 566

<400> SEQUENCE: 566

000

<210> SEQ ID NO 567

<400> SEQUENCE: 567

000

<210> SEQ ID NO 568

<400> SEQUENCE: 568

000

<210> SEQ ID NO 569

<400> SEQUENCE: 569

000

<210> SEQ ID NO 570

<400> SEQUENCE: 570

000

<210> SEQ ID NO 571

<400> SEQUENCE: 571

000

<210> SEQ ID NO 572

<400> SEQUENCE: 572

000

-continued

<210> SEQ ID NO 573

<400> SEQUENCE: 573

000

<210> SEQ ID NO 574

<400> SEQUENCE: 574

000

<210> SEQ ID NO 575

<400> SEQUENCE: 575

000

<210> SEQ ID NO 576

<400> SEQUENCE: 576

000

<210> SEQ ID NO 577

<400> SEQUENCE: 577

000

<210> SEQ ID NO 578

<400> SEQUENCE: 578

000

<210> SEQ ID NO 579

<400> SEQUENCE: 579

000

<210> SEQ ID NO 580

<400> SEQUENCE: 580

000

<210> SEQ ID NO 581

<400> SEQUENCE: 581

000

<210> SEQ ID NO 582

<400> SEQUENCE: 582

000

<210> SEQ ID NO 583

<400> SEQUENCE: 583

-continued

000

<210> SEQ ID NO 584

<400> SEQUENCE: 584

000

<210> SEQ ID NO 585

<400> SEQUENCE: 585

000

<210> SEQ ID NO 586

<400> SEQUENCE: 586

000

<210> SEQ ID NO 587

<400> SEQUENCE: 587

000

<210> SEQ ID NO 588

<400> SEQUENCE: 588

000

<210> SEQ ID NO 589

<400> SEQUENCE: 589

000

<210> SEQ ID NO 590

<400> SEQUENCE: 590

000

<210> SEQ ID NO 591

<400> SEQUENCE: 591

000

<210> SEQ ID NO 592

<400> SEQUENCE: 592

000

<210> SEQ ID NO 593

<400> SEQUENCE: 593

000

<210> SEQ ID NO 594

<400> SEQUENCE: 594

-continued

000

<210> SEQ ID NO 595

<400> SEQUENCE: 595

000

<210> SEQ ID NO 596

<400> SEQUENCE: 596

000

<210> SEQ ID NO 597

<400> SEQUENCE: 597

000

<210> SEQ ID NO 598

<400> SEQUENCE: 598

000

<210> SEQ ID NO 599

<400> SEQUENCE: 599

000

<210> SEQ ID NO 600

<400> SEQUENCE: 600

000

<210> SEQ ID NO 601

<400> SEQUENCE: 601

000

<210> SEQ ID NO 602

<400> SEQUENCE: 602

000

<210> SEQ ID NO 603

<400> SEQUENCE: 603

000

<210> SEQ ID NO 604

<400> SEQUENCE: 604

000

<210> SEQ ID NO 605

-continued

<400> SEQUENCE: 605

000

<210> SEQ ID NO 606
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 606

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 607

<400> SEQUENCE: 607

000

<210> SEQ ID NO 608

<400> SEQUENCE: 608

000

<210> SEQ ID NO 609

<400> SEQUENCE: 609

000

<210> SEQ ID NO 610

<400> SEQUENCE: 610

000

<210> SEQ ID NO 611

<400> SEQUENCE: 611

000

-continued

<210> SEQ ID NO 612

<400> SEQUENCE: 612

000

<210> SEQ ID NO 613

<400> SEQUENCE: 613

000

<210> SEQ ID NO 614

<400> SEQUENCE: 614

000

<210> SEQ ID NO 615

<400> SEQUENCE: 615

000

<210> SEQ ID NO 616
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 616

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
20 25 30

Val Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Glu Ala
65 70 75 80

Glu Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 617

<400> SEQUENCE: 617

000

<210> SEQ ID NO 618

<400> SEQUENCE: 618

000

<210> SEQ ID NO 619

-continued

<400> SEQUENCE: 619

000

<210> SEQ ID NO 620
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 620

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Ile Ser Cys Lys Val Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Trp Met Tyr Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Arg Ile Asp Pro Asn Ser Gly Ser Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Asn Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Tyr Arg Lys Gly Leu Tyr Ala Met Asp Tyr Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 621

<400> SEQUENCE: 621

000

<210> SEQ ID NO 622

<400> SEQUENCE: 622

000

<210> SEQ ID NO 623

<400> SEQUENCE: 623

000

<210> SEQ ID NO 624
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 624

Asp Val Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Leu Gly
1 5 10 15

-continued

```
Gln Pro Ala Ser Ile Ser Cys Lys Ala Ser Gln Asp Val Gly Thr Ala
            20                  25                  30

Val Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Trp Ala Ser Thr Arg His Thr Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Ser Tyr Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

<210> SEQ ID NO 625

<400> SEQUENCE: 625

000

<210> SEQ ID NO 626

<400> SEQUENCE: 626

000

<210> SEQ ID NO 627

<400> SEQUENCE: 627

000

<210> SEQ ID NO 628

<400> SEQUENCE: 628

000

<210> SEQ ID NO 629

<400> SEQUENCE: 629

000

<210> SEQ ID NO 630

<400> SEQUENCE: 630

000

<210> SEQ ID NO 631

<400> SEQUENCE: 631

000

<210> SEQ ID NO 632

<400> SEQUENCE: 632

000

-continued

<210> SEQ ID NO 633

<400> SEQUENCE: 633

000

<210> SEQ ID NO 634

<400> SEQUENCE: 634

000

<210> SEQ ID NO 635

<400> SEQUENCE: 635

000

<210> SEQ ID NO 636

<400> SEQUENCE: 636

000

<210> SEQ ID NO 637

<400> SEQUENCE: 637

000

<210> SEQ ID NO 638

<400> SEQUENCE: 638

000

<210> SEQ ID NO 639

<400> SEQUENCE: 639

000

<210> SEQ ID NO 640

<400> SEQUENCE: 640

000

<210> SEQ ID NO 641

<400> SEQUENCE: 641

000

<210> SEQ ID NO 642

<400> SEQUENCE: 642

000

<210> SEQ ID NO 643

<400> SEQUENCE: 643

000

-continued

<210> SEQ ID NO 644

<400> SEQUENCE: 644

000

<210> SEQ ID NO 645

<400> SEQUENCE: 645

000

<210> SEQ ID NO 646

<400> SEQUENCE: 646

000

<210> SEQ ID NO 647

<400> SEQUENCE: 647

000

<210> SEQ ID NO 648

<400> SEQUENCE: 648

000

<210> SEQ ID NO 649

<400> SEQUENCE: 649

000

<210> SEQ ID NO 650

<400> SEQUENCE: 650

000

<210> SEQ ID NO 651

<400> SEQUENCE: 651

000

<210> SEQ ID NO 652

<400> SEQUENCE: 652

000

<210> SEQ ID NO 653

<400> SEQUENCE: 653

000

<210> SEQ ID NO 654

<400> SEQUENCE: 654

000

-continued

<210> SEQ ID NO 655

<400> SEQUENCE: 655

000

<210> SEQ ID NO 656

<400> SEQUENCE: 656

000

<210> SEQ ID NO 657

<400> SEQUENCE: 657

000

<210> SEQ ID NO 658

<400> SEQUENCE: 658

000

<210> SEQ ID NO 659

<400> SEQUENCE: 659

000

<210> SEQ ID NO 660

<400> SEQUENCE: 660

000

<210> SEQ ID NO 661

<400> SEQUENCE: 661

000

<210> SEQ ID NO 662

<400> SEQUENCE: 662

000

<210> SEQ ID NO 663

<400> SEQUENCE: 663

000

<210> SEQ ID NO 664

<400> SEQUENCE: 664

000

<210> SEQ ID NO 665

<400> SEQUENCE: 665

-continued

000

<210> SEQ ID NO 666

<400> SEQUENCE: 666

000

<210> SEQ ID NO 667

<400> SEQUENCE: 667

000

<210> SEQ ID NO 668

<400> SEQUENCE: 668

000

<210> SEQ ID NO 669

<400> SEQUENCE: 669

000

<210> SEQ ID NO 670

<400> SEQUENCE: 670

000

<210> SEQ ID NO 671

<400> SEQUENCE: 671

000

<210> SEQ ID NO 672

<400> SEQUENCE: 672

000

<210> SEQ ID NO 673

<400> SEQUENCE: 673

000

<210> SEQ ID NO 674

<400> SEQUENCE: 674

000

<210> SEQ ID NO 675

<400> SEQUENCE: 675

000

<210> SEQ ID NO 676

<400> SEQUENCE: 676

-continued

000

<210> SEQ ID NO 677

<400> SEQUENCE: 677

000

<210> SEQ ID NO 678

<400> SEQUENCE: 678

000

<210> SEQ ID NO 679

<400> SEQUENCE: 679

000

<210> SEQ ID NO 680

<400> SEQUENCE: 680

000

<210> SEQ ID NO 681

<400> SEQUENCE: 681

000

<210> SEQ ID NO 682

<400> SEQUENCE: 682

000

<210> SEQ ID NO 683

<400> SEQUENCE: 683

000

<210> SEQ ID NO 684

<400> SEQUENCE: 684

000

<210> SEQ ID NO 685

<400> SEQUENCE: 685

000

<210> SEQ ID NO 686

<400> SEQUENCE: 686

000

<210> SEQ ID NO 687

-continued

<400> SEQUENCE: 687

000

<210> SEQ ID NO 688

<400> SEQUENCE: 688

000

<210> SEQ ID NO 689

<400> SEQUENCE: 689

000

<210> SEQ ID NO 690

<400> SEQUENCE: 690

000

<210> SEQ ID NO 691

<400> SEQUENCE: 691

000

<210> SEQ ID NO 692

<400> SEQUENCE: 692

000

<210> SEQ ID NO 693

<400> SEQUENCE: 693

000

<210> SEQ ID NO 694

<400> SEQUENCE: 694

000

<210> SEQ ID NO 695

<400> SEQUENCE: 695

000

<210> SEQ ID NO 696

<400> SEQUENCE: 696

000

<210> SEQ ID NO 697

<400> SEQUENCE: 697

000

<210> SEQ ID NO 698

-continued

<400> SEQUENCE: 698

000

<210> SEQ ID NO 699

<400> SEQUENCE: 699

000

<210> SEQ ID NO 700

<400> SEQUENCE: 700

000

<210> SEQ ID NO 701

<400> SEQUENCE: 701

000

<210> SEQ ID NO 702

<400> SEQUENCE: 702

000

<210> SEQ ID NO 703

<400> SEQUENCE: 703

000

<210> SEQ ID NO 704

<400> SEQUENCE: 704

000

<210> SEQ ID NO 705

<400> SEQUENCE: 705

000

<210> SEQ ID NO 706
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 706

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Leu Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Arg Gly Gln Arg Leu Glu Trp Ile
35 40 45

Gly Trp Ile Asn Thr Asp Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe

-continued

```
    50                  55                  60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65                  70                  75                  80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asn Pro Pro Tyr Tyr Tyr Gly Thr Asn Asn Ala Glu Ala Met
            100                 105                 110

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120                 125
```

<210> SEQ ID NO 707

<400> SEQUENCE: 707

000

<210> SEQ ID NO 708

<400> SEQUENCE: 708

000

<210> SEQ ID NO 709

<400> SEQUENCE: 709

000

<210> SEQ ID NO 710

<400> SEQUENCE: 710

000

<210> SEQ ID NO 711

<400> SEQUENCE: 711

000

<210> SEQ ID NO 712

<400> SEQUENCE: 712

000

<210> SEQ ID NO 713

<400> SEQUENCE: 713

000

<210> SEQ ID NO 714

<400> SEQUENCE: 714

000

<210> SEQ ID NO 715

<400> SEQUENCE: 715

000

-continued

<210> SEQ ID NO 716

<400> SEQUENCE: 716

000

<210> SEQ ID NO 717

<400> SEQUENCE: 717

000

<210> SEQ ID NO 718
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 718

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ser Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Leu Gln Lys Pro Gly Gln Ser Pro Gln Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Thr Leu His Leu Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Tyr Asn Leu Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 719

<400> SEQUENCE: 719

000

<210> SEQ ID NO 720

<400> SEQUENCE: 720

000

<210> SEQ ID NO 721

<400> SEQUENCE: 721

000

<210> SEQ ID NO 722

<400> SEQUENCE: 722

000

-continued

<210> SEQ ID NO 723

<400> SEQUENCE: 723

000

<210> SEQ ID NO 724
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 724

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Phe Thr Leu Thr Asn Tyr
20 25 30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Asp Thr Gly Glu Pro Thr Tyr Ala Asp Asp Phe
50 55 60

Lys Gly Arg Phe Val Phe Ser Leu Asp Thr Ser Val Ser Thr Ala Tyr
65 70 75 80

Leu Gln Ile Ser Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asn Pro Pro Tyr Tyr Tyr Gly Thr Asn Asn Ala Glu Ala Met
100 105 110

Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 725

<400> SEQUENCE: 725

000

<210> SEQ ID NO 726

<400> SEQUENCE: 726

000

<210> SEQ ID NO 727

<400> SEQUENCE: 727

000

<210> SEQ ID NO 728

<400> SEQUENCE: 728

000

<210> SEQ ID NO 729

<400> SEQUENCE: 729

-continued

000

<210> SEQ ID NO 730
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 730

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Ser Ser Ser Gln Asp Ile Ser Asn Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Tyr Thr Ser Thr Leu His Leu Gly Ile Pro Pro Arg Phe Ser Gly
50 55 60

Ser Gly Tyr Gly Thr Asp Phe Thr Leu Thr Ile Asn Asn Ile Glu Ser
65 70 75 80

Glu Asp Ala Ala Tyr Tyr Phe Cys Gln Gln Tyr Tyr Asn Leu Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 731

<400> SEQUENCE: 731

000

<210> SEQ ID NO 732

<400> SEQUENCE: 732

000

<210> SEQ ID NO 733

<400> SEQUENCE: 733

000

<210> SEQ ID NO 734

<400> SEQUENCE: 734

000

<210> SEQ ID NO 735

<400> SEQUENCE: 735

000

<210> SEQ ID NO 736

<400> SEQUENCE: 736

000

-continued

<210> SEQ ID NO 737

<400> SEQUENCE: 737

000

<210> SEQ ID NO 738

<400> SEQUENCE: 738

000

<210> SEQ ID NO 739

<400> SEQUENCE: 739

000

<210> SEQ ID NO 740

<400> SEQUENCE: 740

000

<210> SEQ ID NO 741

<400> SEQUENCE: 741

000

<210> SEQ ID NO 742

<400> SEQUENCE: 742

000

<210> SEQ ID NO 743

<400> SEQUENCE: 743

000

<210> SEQ ID NO 744

<400> SEQUENCE: 744

000

<210> SEQ ID NO 745

<400> SEQUENCE: 745

000

<210> SEQ ID NO 746

<400> SEQUENCE: 746

000

<210> SEQ ID NO 747

<400> SEQUENCE: 747

-continued

000

<210> SEQ ID NO 748

<400> SEQUENCE: 748

000

<210> SEQ ID NO 749

<400> SEQUENCE: 749

000

<210> SEQ ID NO 750

<400> SEQUENCE: 750

000

<210> SEQ ID NO 751

<400> SEQUENCE: 751

000

<210> SEQ ID NO 752

<400> SEQUENCE: 752

000

<210> SEQ ID NO 753

<400> SEQUENCE: 753

000

<210> SEQ ID NO 754

<400> SEQUENCE: 754

000

<210> SEQ ID NO 755

<400> SEQUENCE: 755

000

<210> SEQ ID NO 756

<400> SEQUENCE: 756

000

<210> SEQ ID NO 757

<400> SEQUENCE: 757

000

<210> SEQ ID NO 758

<400> SEQUENCE: 758

-continued

000

<210> SEQ ID NO 759

<400> SEQUENCE: 759

000

<210> SEQ ID NO 760

<400> SEQUENCE: 760

000

<210> SEQ ID NO 761

<400> SEQUENCE: 761

000

<210> SEQ ID NO 762
<211> LENGTH: 447
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 762

```
Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Phe Ser Asp Tyr
            20                  25                  30

Tyr Trp Asn Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Glu Ile Asn His Arg Gly Ser Thr Asn Ser Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Leu Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Arg Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Phe Gly Tyr Ser Asp Tyr Glu Tyr Asn Trp Phe Asp Pro Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Lys Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro
```

-continued

```
    210                 215                 220

Pro Cys Pro Pro Cys Pro Ala Pro Glu Phe Leu Gly Gly Pro Ser Val
225                 230                 235                 240

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
                245                 250                 255

Pro Glu Val Thr Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu
            260                 265                 270

Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
        275                 280                 285

Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser
    290                 295                 300

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
305                 310                 315                 320

Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile
                325                 330                 335

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
            340                 345                 350

Pro Ser Gln Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
        355                 360                 365

Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn
    370                 375                 380

Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser
385                 390                 395                 400

Asp Gly Ser Phe Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg
                405                 410                 415

Trp Gln Glu Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu
            420                 425                 430

His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440                 445


<210> SEQ ID NO 763
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 763

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gln Gly Thr Asn Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110
```

-continued

```
Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 764
<211> LENGTH: 446
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 764

Gln Val Gln Leu Lys Glu Ser Gly Pro Gly Leu Val Ala Pro Ser Gln
1               5                   10                  15

Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Ala Tyr
            20                  25                  30

Gly Val Asn Trp Val Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45

Gly Met Ile Trp Asp Asp Gly Ser Thr Asp Tyr Asn Ser Ala Leu Lys
    50                  55                  60

Ser Arg Leu Ser Ile Ser Lys Asp Asn Ser Lys Ser Gln Val Phe Leu
65                  70                  75                  80

Lys Met Asn Ser Leu Gln Thr Asp Asp Thr Ala Arg Tyr Tyr Cys Ala
                85                  90                  95

Arg Glu Gly Asp Val Ala Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
            100                 105                 110

Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu
    130                 135                 140

Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly
145                 150                 155                 160

Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser
                165                 170                 175

Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu
            180                 185                 190

Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr
        195                 200                 205

Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr
    210                 215                 220
```

-continued

```
Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 765
<211> LENGTH: 220
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 765

Asp Ile Val Met Thr Gln Ser Pro Ser Ser Leu Ala Val Ser Val Gly
1               5                   10                  15

Gln Lys Val Thr Met Ser Cys Lys Ser Ser Gln Ser Leu Leu Asn Gly
            20                  25                  30

Ser Asn Gln Lys Asn Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
        35                  40                  45

Ser Pro Lys Leu Leu Val Tyr Phe Ala Ser Thr Arg Asp Ser Gly Val
    50                  55                  60

Pro Asp Arg Phe Ile Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65                  70                  75                  80

Ile Ser Ser Val Gln Ala Glu Asp Leu Ala Asp Tyr Phe Cys Leu Gln
                85                  90                  95

His Phe Gly Thr Pro Pro Thr Phe Gly Gly Gly Thr Lys Leu Glu Ile
            100                 105                 110

Lys Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp
```

-continued

```
        115                 120                 125

Glu Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn
    130                 135                 140

Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu
145                 150                 155                 160

Gln Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp
                165                 170                 175

Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr
            180                 185                 190

Glu Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser
        195                 200                 205

Ser Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
    210                 215                 220


<210> SEQ ID NO 766

<400> SEQUENCE: 766

000


<210> SEQ ID NO 767

<400> SEQUENCE: 767

000


<210> SEQ ID NO 768

<400> SEQUENCE: 768

000


<210> SEQ ID NO 769

<400> SEQUENCE: 769

000


<210> SEQ ID NO 770

<400> SEQUENCE: 770

000


<210> SEQ ID NO 771

<400> SEQUENCE: 771

000


<210> SEQ ID NO 772

<400> SEQUENCE: 772

000


<210> SEQ ID NO 773

<400> SEQUENCE: 773

000
```

-continued

<210> SEQ ID NO 774

<400> SEQUENCE: 774

000

<210> SEQ ID NO 775

<400> SEQUENCE: 775

000

<210> SEQ ID NO 776

<400> SEQUENCE: 776

000

<210> SEQ ID NO 777

<400> SEQUENCE: 777

000

<210> SEQ ID NO 778

<400> SEQUENCE: 778

000

<210> SEQ ID NO 779

<400> SEQUENCE: 779

000

<210> SEQ ID NO 780

<400> SEQUENCE: 780

000

<210> SEQ ID NO 781

<400> SEQUENCE: 781

000

<210> SEQ ID NO 782

<400> SEQUENCE: 782

000

<210> SEQ ID NO 783

<400> SEQUENCE: 783

000

<210> SEQ ID NO 784

<400> SEQUENCE: 784

000

-continued

<210> SEQ ID NO 785

<400> SEQUENCE: 785

000

<210> SEQ ID NO 786

<400> SEQUENCE: 786

000

<210> SEQ ID NO 787

<400> SEQUENCE: 787

000

<210> SEQ ID NO 788

<400> SEQUENCE: 788

000

<210> SEQ ID NO 789

<400> SEQUENCE: 789

000

<210> SEQ ID NO 790

<400> SEQUENCE: 790

000

<210> SEQ ID NO 791

<400> SEQUENCE: 791

000

<210> SEQ ID NO 792

<400> SEQUENCE: 792

000

<210> SEQ ID NO 793

<400> SEQUENCE: 793

000

<210> SEQ ID NO 794

<400> SEQUENCE: 794

000

<210> SEQ ID NO 795

<400> SEQUENCE: 795

-continued

000

<210> SEQ ID NO 796

<400> SEQUENCE: 796

000

<210> SEQ ID NO 797

<400> SEQUENCE: 797

000

<210> SEQ ID NO 798

<400> SEQUENCE: 798

000

<210> SEQ ID NO 799

<400> SEQUENCE: 799

000

<210> SEQ ID NO 800

<400> SEQUENCE: 800

000

<210> SEQ ID NO 801

<400> SEQUENCE: 801

000

<210> SEQ ID NO 802

<400> SEQUENCE: 802

000

<210> SEQ ID NO 803

<400> SEQUENCE: 803

000

<210> SEQ ID NO 804

<400> SEQUENCE: 804

000

<210> SEQ ID NO 805

<400> SEQUENCE: 805

000

<210> SEQ ID NO 806
<211> LENGTH: 118
<212> TYPE: PRT

-continued

<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 806

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Asp Ile Tyr Pro Gly Asn Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Val Thr Ile Thr Ala Asp Lys Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Gly Ala Phe Pro Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 807

<400> SEQUENCE: 807

000

<210> SEQ ID NO 808

<400> SEQUENCE: 808

000

<210> SEQ ID NO 809

<400> SEQUENCE: 809

000

<210> SEQ ID NO 810

<400> SEQUENCE: 810

000

<210> SEQ ID NO 811

<400> SEQUENCE: 811

000

<210> SEQ ID NO 812

<400> SEQUENCE: 812

000

<210> SEQ ID NO 813

-continued

<400> SEQUENCE: 813

000

<210> SEQ ID NO 814

<400> SEQUENCE: 814

000

<210> SEQ ID NO 815

<400> SEQUENCE: 815

000

<210> SEQ ID NO 816
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 816

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Ser
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ser Arg
85 90 95

Lys Asp Pro Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 817

<400> SEQUENCE: 817

000

<210> SEQ ID NO 818

<400> SEQUENCE: 818

000

<210> SEQ ID NO 819

<400> SEQUENCE: 819

000

<210> SEQ ID NO 820

-continued

<400> SEQUENCE: 820

000

<210> SEQ ID NO 821

<400> SEQUENCE: 821

000

<210> SEQ ID NO 822
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 822

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30

Asn Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

Gly Asp Ile Tyr Pro Gly Gln Gly Asp Thr Ser Tyr Asn Gln Lys Phe
50 55 60

Lys Gly Arg Ala Thr Met Thr Ala Asp Lys Ser Thr Ser Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Val Gly Gly Ala Phe Pro Met Asp Tyr Trp Gly Gln Gly Thr
100 105 110

Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 823

<400> SEQUENCE: 823

000

<210> SEQ ID NO 824

<400> SEQUENCE: 824

000

<210> SEQ ID NO 825

<400> SEQUENCE: 825

000

<210> SEQ ID NO 826
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:

-continued

Synthetic polypeptide"

<400> SEQUENCE: 826

Asp Ile Val Leu Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Arg Ala Ser Glu Ser Val Glu Tyr Tyr
20 25 30

Gly Thr Ser Leu Met Gln Trp Tyr Gln Gln Lys Pro Gly Gln Pro Pro
35 40 45

Lys Leu Leu Ile Tyr Ala Ala Ser Asn Val Glu Ser Gly Val Pro Asp
50 55 60

Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser
65 70 75 80

Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln Ser Arg
85 90 95

Lys Asp Pro Ser Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 827

<400> SEQUENCE: 827

000

<210> SEQ ID NO 828

<400> SEQUENCE: 828

000

<210> SEQ ID NO 829

<400> SEQUENCE: 829

000

<210> SEQ ID NO 830
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 830

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ala Ser Gly Phe Thr Phe Ser Ser
20 25 30

Tyr Asp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp
35 40 45

Val Ser Thr Ile Ser Gly Gly Gly Thr Tyr Thr Tyr Tyr Gln Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95

-continued

Cys Ala Ser Met Asp Tyr Trp Gly Gln Gly Thr Thr Val Thr Val Ser
100 105 110

Ser Ala

<210> SEQ ID NO 831
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 831

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Arg Arg Tyr
20 25 30

Leu Asn Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Ser His Ser Ala Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 832
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 832

Glu Val Gln Val Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Tyr Cys Val Ala Ser Gly Phe Thr Phe Ser Gly Ser
20 25 30

Tyr Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp
35 40 45

Val Ser Ala Ile Ser Gly Ser Gly Gly Ser Thr Tyr Tyr Ala Asp Ser
50 55 60

Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu
65 70 75 80

Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Lys Lys Tyr Tyr Val Gly Pro Ala Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser Gly
115 120

<210> SEQ ID NO 833

-continued

<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 833

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Ser Val Leu Tyr Ser
20 25 30

Ser Asn Asn Lys Asn Tyr Leu Ala Trp Tyr Gln His Lys Pro Gly Gln
35 40 45

Pro Pro Lys Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Ser Pro Leu Thr Phe Gly Gly Gly Thr Lys Ile Glu Val
100 105 110

Lys

<210> SEQ ID NO 834

<400> SEQUENCE: 834

000

<210> SEQ ID NO 835

<400> SEQUENCE: 835

000

<210> SEQ ID NO 836

<400> SEQUENCE: 836

000

<210> SEQ ID NO 837

<400> SEQUENCE: 837

000

<210> SEQ ID NO 838

<400> SEQUENCE: 838

000

<210> SEQ ID NO 839

<400> SEQUENCE: 839

000

-continued

<210> SEQ ID NO 840

<400> SEQUENCE: 840

000

<210> SEQ ID NO 841

<400> SEQUENCE: 841

000

<210> SEQ ID NO 842

<400> SEQUENCE: 842

000

<210> SEQ ID NO 843

<400> SEQUENCE: 843

000

<210> SEQ ID NO 844

<400> SEQUENCE: 844

000

<210> SEQ ID NO 845

<400> SEQUENCE: 845

000

<210> SEQ ID NO 846

<400> SEQUENCE: 846

000

<210> SEQ ID NO 847

<400> SEQUENCE: 847

000

<210> SEQ ID NO 848

<400> SEQUENCE: 848

000

<210> SEQ ID NO 849

<400> SEQUENCE: 849

000

<210> SEQ ID NO 850

<400> SEQUENCE: 850

000

-continued

<210> SEQ ID NO 851

<400> SEQUENCE: 851

000

<210> SEQ ID NO 852

<400> SEQUENCE: 852

000

<210> SEQ ID NO 853

<400> SEQUENCE: 853

000

<210> SEQ ID NO 854

<400> SEQUENCE: 854

000

<210> SEQ ID NO 855

<400> SEQUENCE: 855

000

<210> SEQ ID NO 856

<400> SEQUENCE: 856

000

<210> SEQ ID NO 857

<400> SEQUENCE: 857

000

<210> SEQ ID NO 858

<400> SEQUENCE: 858

000

<210> SEQ ID NO 859

<400> SEQUENCE: 859

000

<210> SEQ ID NO 860

<400> SEQUENCE: 860

000

<210> SEQ ID NO 861

<400> SEQUENCE: 861

000

-continued

<210> SEQ ID NO 862

<400> SEQUENCE: 862

000

<210> SEQ ID NO 863

<400> SEQUENCE: 863

000

<210> SEQ ID NO 864

<400> SEQUENCE: 864

000

<210> SEQ ID NO 865

<400> SEQUENCE: 865

000

<210> SEQ ID NO 866

<400> SEQUENCE: 866

000

<210> SEQ ID NO 867

<400> SEQUENCE: 867

000

<210> SEQ ID NO 868

<400> SEQUENCE: 868

000

<210> SEQ ID NO 869

<400> SEQUENCE: 869

000

<210> SEQ ID NO 870

<400> SEQUENCE: 870

000

<210> SEQ ID NO 871

<400> SEQUENCE: 871

000

<210> SEQ ID NO 872

<400> SEQUENCE: 872

-continued

000

<210> SEQ ID NO 873

<400> SEQUENCE: 873

000

<210> SEQ ID NO 874

<400> SEQUENCE: 874

000

<210> SEQ ID NO 875

<400> SEQUENCE: 875

000

<210> SEQ ID NO 876

<400> SEQUENCE: 876

000

<210> SEQ ID NO 877

<400> SEQUENCE: 877

000

<210> SEQ ID NO 878

<400> SEQUENCE: 878

000

<210> SEQ ID NO 879

<400> SEQUENCE: 879

000

<210> SEQ ID NO 880

<400> SEQUENCE: 880

000

<210> SEQ ID NO 881

<400> SEQUENCE: 881

000

<210> SEQ ID NO 882

<400> SEQUENCE: 882

000

<210> SEQ ID NO 883

<400> SEQUENCE: 883

-continued

000

<210> SEQ ID NO 884

<400> SEQUENCE: 884

000

<210> SEQ ID NO 885

<400> SEQUENCE: 885

000

<210> SEQ ID NO 886

<400> SEQUENCE: 886

000

<210> SEQ ID NO 887

<400> SEQUENCE: 887

000

<210> SEQ ID NO 888

<400> SEQUENCE: 888

000

<210> SEQ ID NO 889

<400> SEQUENCE: 889

000

<210> SEQ ID NO 890

<400> SEQUENCE: 890

000

<210> SEQ ID NO 891

<400> SEQUENCE: 891

000

<210> SEQ ID NO 892

<400> SEQUENCE: 892

000

<210> SEQ ID NO 893

<400> SEQUENCE: 893

000

<210> SEQ ID NO 894

-continued

<400> SEQUENCE: 894

000

<210> SEQ ID NO 895

<400> SEQUENCE: 895

000

<210> SEQ ID NO 896

<400> SEQUENCE: 896

000

<210> SEQ ID NO 897

<400> SEQUENCE: 897

000

<210> SEQ ID NO 898

<400> SEQUENCE: 898

000

<210> SEQ ID NO 899

<400> SEQUENCE: 899

000

<210> SEQ ID NO 900

<400> SEQUENCE: 900

000

<210> SEQ ID NO 901
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 901

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Ser Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Ser Leu Ser Ser Tyr
20 25 30

Gly Val Asp Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Gly Val Ile Trp Gly Gly Gly Gly Thr Tyr Tyr Ala Ser Ser Leu Met
50 55 60

Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu
65 70 75 80

Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

-continued

```
Arg His Ala Tyr Gly His Asp Gly Gly Phe Ala Met Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 902
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 902

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1               5                   10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Glu Ser Val Ser Ser Asn
            20                  25                  30

Val Ala Trp Tyr Gln Gln Arg Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu Pro
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gly Gln Ser Tyr Ser Tyr Pro Phe
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 903

<400> SEQUENCE: 903

000


<210> SEQ ID NO 904

<400> SEQUENCE: 904

000


<210> SEQ ID NO 905

<400> SEQUENCE: 905

000


<210> SEQ ID NO 906

<400> SEQUENCE: 906

000


<210> SEQ ID NO 907

<400> SEQUENCE: 907

000


<210> SEQ ID NO 908
```

-continued

<400> SEQUENCE: 908

000

<210> SEQ ID NO 909

<400> SEQUENCE: 909

000

<210> SEQ ID NO 910

<400> SEQUENCE: 910

000

<210> SEQ ID NO 911

<400> SEQUENCE: 911

000

<210> SEQ ID NO 912

<400> SEQUENCE: 912

000

<210> SEQ ID NO 913

<400> SEQUENCE: 913

000

<210> SEQ ID NO 914

<400> SEQUENCE: 914

000

<210> SEQ ID NO 915

<400> SEQUENCE: 915

000

<210> SEQ ID NO 916

<400> SEQUENCE: 916

000

<210> SEQ ID NO 917

<400> SEQUENCE: 917

000

<210> SEQ ID NO 918

<400> SEQUENCE: 918

000

-continued

<210> SEQ ID NO 919

<400> SEQUENCE: 919

000

<210> SEQ ID NO 920
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 920

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Glu Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Gly Ser Met Val Arg Gly Asp Tyr Tyr Tyr Gly Met Asp
100 105 110

Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 921
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 921

Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Ala
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

-continued

<210> SEQ ID NO 922

<400> SEQUENCE: 922

000

<210> SEQ ID NO 923

<400> SEQUENCE: 923

000

<210> SEQ ID NO 924

<400> SEQUENCE: 924

000

<210> SEQ ID NO 925

<400> SEQUENCE: 925

000

<210> SEQ ID NO 926

<400> SEQUENCE: 926

000

<210> SEQ ID NO 927

<400> SEQUENCE: 927

000

<210> SEQ ID NO 928

<400> SEQUENCE: 928

000

<210> SEQ ID NO 929

<400> SEQUENCE: 929

000

<210> SEQ ID NO 930

<400> SEQUENCE: 930

000

<210> SEQ ID NO 931

<400> SEQUENCE: 931

000

<210> SEQ ID NO 932

<400> SEQUENCE: 932

000

-continued

<210> SEQ ID NO 933

<400> SEQUENCE: 933

000

<210> SEQ ID NO 934

<400> SEQUENCE: 934

000

<210> SEQ ID NO 935

<400> SEQUENCE: 935

000

<210> SEQ ID NO 936

<400> SEQUENCE: 936

000

<210> SEQ ID NO 937

<400> SEQUENCE: 937

000

<210> SEQ ID NO 938

<400> SEQUENCE: 938

000

<210> SEQ ID NO 939

<400> SEQUENCE: 939

000

<210> SEQ ID NO 940

<400> SEQUENCE: 940

000

<210> SEQ ID NO 941

<400> SEQUENCE: 941

000

<210> SEQ ID NO 942

<400> SEQUENCE: 942

000

<210> SEQ ID NO 943

<400> SEQUENCE: 943

000

-continued

<210> SEQ ID NO 944

<400> SEQUENCE: 944

000

<210> SEQ ID NO 945

<400> SEQUENCE: 945

000

<210> SEQ ID NO 946

<400> SEQUENCE: 946

000

<210> SEQ ID NO 947

<400> SEQUENCE: 947

000

<210> SEQ ID NO 948

<400> SEQUENCE: 948

000

<210> SEQ ID NO 949

<400> SEQUENCE: 949

000

<210> SEQ ID NO 950

<400> SEQUENCE: 950

000

<210> SEQ ID NO 951

<400> SEQUENCE: 951

000

<210> SEQ ID NO 952

<400> SEQUENCE: 952

000

<210> SEQ ID NO 953

<400> SEQUENCE: 953

000

<210> SEQ ID NO 954

<400> SEQUENCE: 954

-continued

000

<210> SEQ ID NO 955

<400> SEQUENCE: 955

000

<210> SEQ ID NO 956

<400> SEQUENCE: 956

000

<210> SEQ ID NO 957

<400> SEQUENCE: 957

000

<210> SEQ ID NO 958

<400> SEQUENCE: 958

000

<210> SEQ ID NO 959

<400> SEQUENCE: 959

000

<210> SEQ ID NO 960

<400> SEQUENCE: 960

000

<210> SEQ ID NO 961

<400> SEQUENCE: 961

000

<210> SEQ ID NO 962

<400> SEQUENCE: 962

000

<210> SEQ ID NO 963

<400> SEQUENCE: 963

000

<210> SEQ ID NO 964

<400> SEQUENCE: 964

000

<210> SEQ ID NO 965

<400> SEQUENCE: 965

-continued

000

<210> SEQ ID NO 966

<400> SEQUENCE: 966

000

<210> SEQ ID NO 967

<400> SEQUENCE: 967

000

<210> SEQ ID NO 968

<400> SEQUENCE: 968

000

<210> SEQ ID NO 969

<400> SEQUENCE: 969

000

<210> SEQ ID NO 970

<400> SEQUENCE: 970

000

<210> SEQ ID NO 971

<400> SEQUENCE: 971

000

<210> SEQ ID NO 972

<400> SEQUENCE: 972

000

<210> SEQ ID NO 973

<400> SEQUENCE: 973

000

<210> SEQ ID NO 974

<400> SEQUENCE: 974

000

<210> SEQ ID NO 975

<400> SEQUENCE: 975

000

<210> SEQ ID NO 976

-continued

<400> SEQUENCE: 976

000

<210> SEQ ID NO 977

<400> SEQUENCE: 977

000

<210> SEQ ID NO 978

<400> SEQUENCE: 978

000

<210> SEQ ID NO 979

<400> SEQUENCE: 979

000

<210> SEQ ID NO 980

<400> SEQUENCE: 980

000

<210> SEQ ID NO 981

<400> SEQUENCE: 981

000

<210> SEQ ID NO 982

<400> SEQUENCE: 982

000

<210> SEQ ID NO 983

<400> SEQUENCE: 983

000

<210> SEQ ID NO 984

<400> SEQUENCE: 984

000

<210> SEQ ID NO 985

<400> SEQUENCE: 985

000

<210> SEQ ID NO 986

<400> SEQUENCE: 986

000

<210> SEQ ID NO 987

-continued

<400> SEQUENCE: 987

000

<210> SEQ ID NO 988

<400> SEQUENCE: 988

000

<210> SEQ ID NO 989

<400> SEQUENCE: 989

000

<210> SEQ ID NO 990

<400> SEQUENCE: 990

000

<210> SEQ ID NO 991

<400> SEQUENCE: 991

000

<210> SEQ ID NO 992

<400> SEQUENCE: 992

000

<210> SEQ ID NO 993

<400> SEQUENCE: 993

000

<210> SEQ ID NO 994

<400> SEQUENCE: 994

000

<210> SEQ ID NO 995

<400> SEQUENCE: 995

000

<210> SEQ ID NO 996

<400> SEQUENCE: 996

000

<210> SEQ ID NO 997

<400> SEQUENCE: 997

000

-continued

<210> SEQ ID NO 998

<400> SEQUENCE: 998

000

<210> SEQ ID NO 999

<400> SEQUENCE: 999

000

<210> SEQ ID NO 1000

<400> SEQUENCE: 1000

000

<210> SEQ ID NO 1001
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1001

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> SEQ ID NO 1002
<211> LENGTH: 170
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 1002

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro Ser Thr Val
65 70 75 80

Thr Thr Ala Gly Val Thr Pro Gln Pro Glu Ser Leu Ser Pro Ser Gly
85 90 95

-continued

Lys Glu Pro Ala Ala Ser Ser Pro Ser Ser Asn Asn Thr Ala Ala Thr
100 105 110

Thr Ala Ala Ile Val Pro Gly Ser Gln Leu Met Pro Ser Lys Ser Pro
115 120 125

Ser Thr Gly Thr Thr Glu Ile Ser Ser His Glu Ser Ser His Gly Thr
130 135 140

Pro Ser Gln Thr Thr Ala Lys Asn Trp Glu Leu Thr Ala Ser Ala Ser
145 150 155 160

His Gln Pro Pro Gly Val Tyr Pro Gln Gly
165 170

<210> SEQ ID NO 1003
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1003

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1 5 10 15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
20 25 30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
35 40 45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
50 55 60

Asn Leu Ile Ile Leu Ala Asn Asp Ser Leu Ser Ser Asn Gly Asn Val
65 70 75 80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
85 90 95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
100 105 110

Thr Ser

<210> SEQ ID NO 1004
<211> LENGTH: 297
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
Synthetic polypeptide"

<400> SEQUENCE: 1004

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1 5 10 15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
20 25 30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
35 40 45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
50 55 60

Arg Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro

-continued

```
65                  70                  75                  80

Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys
                85                  90                  95

Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val
            100                 105                 110

Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr
        115                 120                 125

Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu
    130                 135                 140

Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His
145                 150                 155                 160

Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys
                165                 170                 175

Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln
            180                 185                 190

Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu
        195                 200                 205

Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro
    210                 215                 220

Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn
225                 230                 235                 240

Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu
                245                 250                 255

Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val
            260                 265                 270

Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln
        275                 280                 285

Lys Ser Leu Ser Leu Ser Pro Gly Lys
    290                 295


<210> SEQ ID NO 1005
<211> LENGTH: 114
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (93)..(93)
<223> OTHER INFORMATION: /replace="Lys"
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(114)
<223> OTHER INFORMATION: /note="Variant residues given in the sequence
      have no preference with respect to those in the annotations
      for variant positions"

<400> SEQUENCE: 1005

Asn Trp Val Asn Val Ile Ser Asp Leu Lys Lys Ile Glu Asp Leu Ile
1               5                   10                  15

Gln Ser Met His Ile Asp Ala Thr Leu Tyr Thr Glu Ser Asp Val His
            20                  25                  30

Pro Ser Cys Lys Val Thr Ala Met Lys Cys Phe Leu Leu Glu Leu Gln
        35                  40                  45

Val Ile Ser Leu Glu Ser Gly Asp Ala Ser Ile His Asp Thr Val Glu
```

-continued

```
    50                  55                  60

Asn Leu Ile Ile Leu Ala Asn Asn Ser Leu Ser Ser Asn Gly Asn Val
65                  70                  75                  80

Thr Glu Ser Gly Cys Lys Glu Cys Glu Glu Leu Glu Glu Lys Asn Ile
                85                  90                  95

Lys Glu Phe Leu Gln Ser Phe Val His Ile Val Gln Met Phe Ile Asn
            100                 105                 110

Thr Ser


<210> SEQ ID NO 1006
<211> LENGTH: 77
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 1006

Ile Thr Cys Pro Pro Pro Met Ser Val Glu His Ala Asp Ile Trp Val
1               5                   10                  15

Lys Ser Tyr Ser Leu Tyr Ser Arg Glu Arg Tyr Ile Cys Asn Ser Gly
            20                  25                  30

Phe Lys Arg Lys Ala Gly Thr Ser Ser Leu Thr Glu Cys Val Leu Asn
        35                  40                  45

Lys Ala Thr Asn Val Ala His Trp Thr Thr Pro Ser Leu Lys Cys Ile
    50                  55                  60

Arg Asp Pro Ala Leu Val His Gln Arg Pro Ala Pro Pro
65                  70                  75


<210> SEQ ID NO 1007
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 1007

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
            20                  25                  30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65                  70                  75                  80

Glu Asp Ala Ala Ala Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125
```

-continued

```
Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 1008
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 1008

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Val Tyr
            20                  25                  30

Gly Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Ile Ile Trp Tyr Asp Gly Asp Asn Gln Tyr Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Gly Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Asp Leu Arg Thr Gly Pro Phe Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro
        115                 120                 125

Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly
    130                 135                 140

Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp Asn
145                 150                 155                 160

Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu Gln
                165                 170                 175

Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser Ser
            180                 185                 190

Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro Ser
        195                 200                 205

Asn Thr Lys Val Asp Lys Arg Val Glu Pro Lys Ser Cys Asp Lys Thr
    210                 215                 220

His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
```

-continued

```
               245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445


<210> SEQ ID NO 1009
<211> LENGTH: 445
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 1009

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Ser Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Gly Val Gly Trp Ile Arg Gln Pro Ser Gly Lys Gly Leu Glu
        35                  40                  45

Trp Leu Ala His Ile Trp Trp Asp Gly Asp Glu Ser Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Ser Leu Lys Ile Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Phe
                85                  90                  95

Cys Ala Arg Asn Arg Tyr Asp Pro Pro Trp Phe Val Asp Trp Gly Gln
            100                 105                 110

Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala
    130                 135                 140
```

-continued

```
Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Thr
            180                 185                 190

Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys Cys Val
    210                 215                 220

Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser Val Phe
225                 230                 235                 240

Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro
                245                 250                 255

Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu Val
            260                 265                 270

Gln Phe Asn Trp Tyr Val Asp Gly Met Glu Val His Asn Ala Lys Thr
        275                 280                 285

Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val Ser Val
    290                 295                 300

Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys
305                 310                 315                 320

Lys Val Ser Asn Lys Gly Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser
                325                 330                 335

Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro
            340                 345                 350

Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val
        355                 360                 365

Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly
    370                 375                 380

Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp Ser Asp
385                 390                 395                 400

Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp
                405                 410                 415

Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His
            420                 425                 430

Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
        435                 440                 445


<210> SEQ ID NO 1010
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: source
<223> OTHER INFORMATION: /note="Description of Artificial Sequence:
      Synthetic polypeptide"

<400> SEQUENCE: 1010

Asp Ile Gln Met Thr Gln Ser Thr Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Asn Tyr
            20                  25                  30
```

-continued

```
Leu Ser Trp Tyr Gln Gln Lys Pro Gly Lys Ala Val Lys Leu Leu Ile
        35                  40                  45

Tyr Tyr Thr Ser Lys Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Ser Ser Leu Gln Gln
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Phe Cys Leu Gln Gly Lys Met Leu Pro Trp
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

1. A method of treating a cancer having at least a partial inflammatory basis, comprising administering a therapeutically effective amount of an IL-1β inhibitor to a patient in need, wherein the patient has high sensitivity C-reactive protein (hsCRP) concentration equal to or greater than about 2 mg/L before first administration of the inhibitor.

2. The method of claim **1**, wherein the IL-1β inhibitor is canakinumab or gevokizumab.

3. The method of claim **1** wherein the cancer having at least a partial inflammatory basis is lung cancer.

4. The method of claim **1**, wherein the patient has high sensitivity C-reactive protein (hsCRP) equal to or greater than 10 mg/L before first administration of canakinumab.

5. The method of claim **4**, wherein the high sensitivity C-reactive protein (hsCRP) level of the patient has reduced to below about 2.3 mg/L assessed at least about 3 months after first administration of canakinumab.

6. The method of claim **4**, wherein the high sensitivity C-reactive protein (hsCRP) level of the patient has reduced to below about 2 mg/L assessed at least about 3 months after first administration of canakinumab.

7. The method of claim **1**, wherein the high sensitivity C-reactive protein (hsCRP) level of the patient has reduced to below about 1.8 mg/L assessed at least about 3 months after first administration of canakinumab.

8. The method of claim **3**, wherein the high sensitivity C-reactive protein (hsCRP) level of the patient has reduced to below about 1.8 mg/L assessed at least about 3 months after first administration of canakinumab.

9. The method of claim **1**, wherein the high sensitivity C-reactive protein (hsCRP) level of the patient has reduced by at least 20% compared to baseline assessed at least about 3 months after first administration of the IL-1β inhibitor.

10. The method of claim **1**, wherein the interleukin-6 (IL-6) level of said patient has reduced by at least 20% compared to baseline assessed at least about 3 months after first administration of the IL-1β inhibitor.

11. The method of claim **2** wherein the therapeutically effective amount of canakinumab is about 90 mg to about 450 mg of canakinumab.

12. The method of claim **2**, wherein the therapeutically effective amount of canakinumab is about 200 mg to about 450 mg.

13. The method of claim **2**, wherein the therapeutically effective amount of canakinumab is about 200 mg of canakinumab.

14. The method of claim **2**, wherein canakinumab is administered every two, three or four weeks (monthly).

15. The method of claim **2**, wherein canakinumab is administered subcutaneously.

16. The method of claim **2**, wherein canakinumab is administered intravenously.

17. The method of claim **2**, wherein canakinumab is administered in a liquid form contained in a prefilled syringe or as a lyophilized form for reconstitution.

18. The method of claim **2**, wherein 200 mg canakinumab is administered subcutaneously every three weeks.

19. The method of claim **2**, wherein canakinumab is administered in combination with one or more therapeutic agents.

20. The method of claim **19**, wherein the therapeutic agent is a platinum based chemotherapy or a platinum-based doublet chemotherapy (PT-DC).

21. The method of claim **19**, wherein the therapeutic agent is a tyrosine kinase inhibitor.

22. The method of claim **19**, wherein the therapeutic agent is a checkpoint inhibitor.

23. The method of claim **19**, wherein the therapeutic agent is a PD-1 or PD-L1 inhibitor selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and spartalizumab (PDR-001).

24. The method of claim **1** wherein the cancer having at least a partial inflammatory basis is a cancer selected from the group consisting of lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), melanoma, gastric or intestinal cancer, esophageal cancer, renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma and biliary tract cancer.

25. A method of treating a cancer having at least a partial inflammatory basis, comprising administering about 90 mg to about 450 mg of an IL-1β inhibitor to a patient in need.

26. The method of claim **25** wherein the IL-1β inhibitor is canakinumab or gevokizumab.

27. The method of claim **25**, wherein the IL-1β inhibitor is administered every 2, 3 or 4 weeks.

28. The method of claim **25** wherein the cancer having at least a partial inflammatory basis is a cancer selected from the group consisting of lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), melanoma, gastric or intestinal cancer, esophageal cancer, renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma and biliary tract cancer.

29. A method of treating a cancer having at least a partial inflammatory basis, comprising administering gevokizumab to a patient in need.

30. The method of claim **29** wherein the cancer having at least a partial inflammatory basis is a cancer selected from the group consisting of lung cancer, non-small cell lung cancer (NSCLC), colorectal cancer (CRC), melanoma, gastric or intestinal cancer, esophageal cancer, renal cell carcinoma (RCC), breast cancer, prostate cancer, head and neck cancer, bladder cancer, hepatocellular carcinoma (HCC), ovarian cancer, cervical cancer, endometrial cancer, pancreatic cancer, neuroendocrine cancer, multiple myeloma and biliary tract cancer.

31. The method of claim **29**, wherein gevokizumab is administered intravenously.

32. The method of claim **29**, wherein gevokizumab is administered every 3 or 4 weeks.

33. The method of claim **29**, wherein about 90 mg to 270 mg of gevokizumab is adminstered.

34. The method of claim **29**, wherein about 90 mg to about 120 mg of gevokizumab is administered.

35. The method of claim **29**, wherein one or more therapeutic agents are administered in addition to gevokizumab.

36. The method of claim **35**, wherein the therapeutic agent is a checkpoint inhibitor.

37. The method of claim **36**, wherein the therapeutic agent is a PD-1 or PD-L1 inhibitor selected from the group consisting of nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab and spartalizumab (PDR-001).

* * * * *